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THE HYALINE MEMBRANE IN THE LUNGS

I. A DESCRIPTIVE STUDY

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A peculiar eosin-staining membrane—the so-called hyaline membrane—lining the walls of bronchioles and alveoli was noted in the lungs of patients who died of influenza in the epidemic of 1918. This formation was so frequently seen that it was considered pathognomonic of the disease. Recently, we have seen the same pathologic picture under such a variety of circumstances that it seems advisable to reconsider the subject.

GENERAL CONSIDERATIONS

The acute, or "fulminating," type of influenzal pneumonia was one of the most interesting manifestations of the disease as seen in the last epidemic, and it attracted the attention of a number of American workers. Winternitz [1] noted an average duration of nine days for this form of pneumonia. According to other observers, it varied in duration from three to twenty days. The lungs, as seen at postmortem examination, were airless and distended with a bloody, serous fluid. The pleural surfaces were mottled with brilliant colors. Occasional large areas of hemorrhage suggested infarcts. Emphysema was often a striking feature, extending into the mediastinal tissues. It was particularly in this type of pneumonia that the hyaline membrane was noted.

As the observations were summarized by Opie [2] in a recent review, this hyaline material may form a continuous layer resting on the walls of the alveolar ducts and extending across the orifices of the tributary alveoli, and may be found similarly placed within alveolar sacs (fig. 1).

It is interesting to note that although the hyaline membrane was described by a number of American workers after the last epidemic, no description of it can be found in the German literature dealing with the epidemic. In an excellent recent review of the German literature by

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1. Winternitz, M. C.; Wason, I. M., and McNamara, F. P.: The Pathology of Influenza, New Haven, Conn., Yale University Press, 1920.

2. Opie, E. L.: Arch. Path. **5**:284, 1928.

Luksch,[3] description of such a histologic picture is conspicuously lacking. Pseudomembranes composed of purulent exudate applied to the mucosal surface of the larynx, trachea and bronchi in cases of influenza were described by Meyer,[4] Stettner [5] and others, but the descriptions do not apply to the hyaline membranes seen in this country.

In the American literature dealing with the hyaline membrane there is a marked lack of agreement in regard to the significance of the picture, the composition of the membrane and the mechanism of its

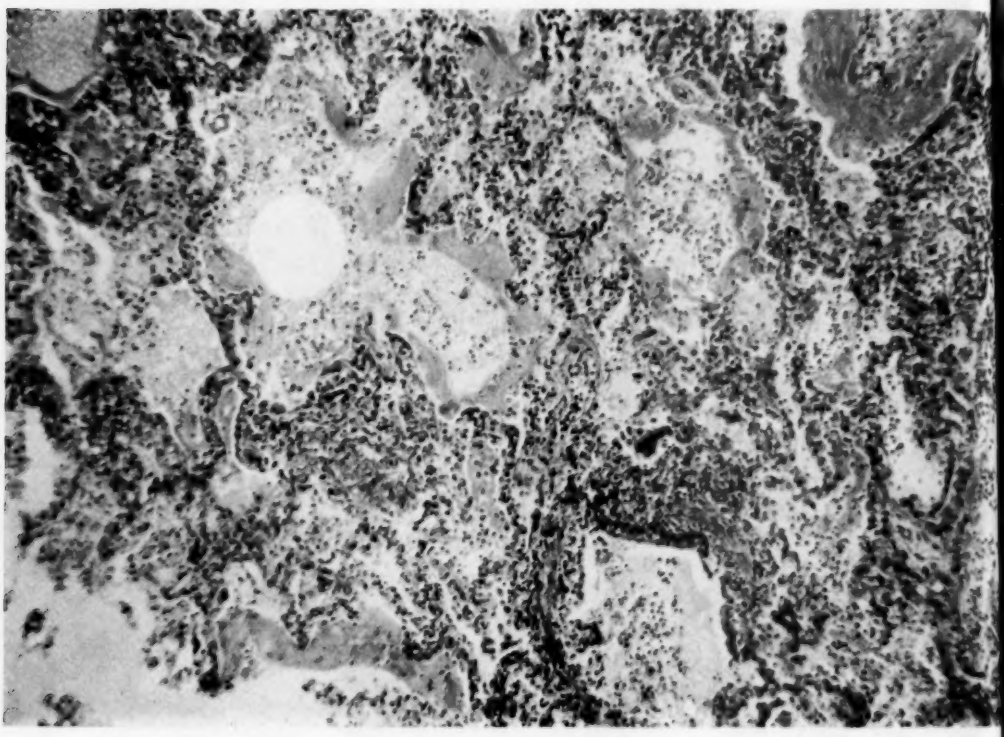

Fig. 1.—Photomicrograph of lung from an adult who died of acute influenzal bronchopneumonia. Note the eosin-staining hyaline membranes. Hematoxylin and eosin; reduced from a magnification of × 112.

formation. It has been variously described as a fibrin or a fibrinoid deposit, the "lesion of characterization" of influenza, and the "virus lesion" distinct from the changes due to secondary pathogenic invaders.

The various explanations regarding the mechanism of the formation of the hyaline membrane can be divided into three main groups: (1)

3. Luksch, Franz: Arch. Path. **5**:448, 1928.
4. Meyer, S.: Deutsche med. Wchnschr. **45**:38, 1919.
5. Stettner, E.: München. med. Wchnschr. **32**:872, 1918.

that in which the membrane is regarded as the result of hyalinization of necrotic alveolar walls, (2) that in which it is considered to be the result of injury to the capillary bed and (3) that in which it is held to be the result of air forced into exudate.

Winternitz and his associates, in a series of communications,[6] attributed the membrane to hyalinization of the necrotic material resulting from the action of some powerful agent on the alveolar walls. They described the membrane as a swollen, homogeneously staining material, quite without architecture, replacing the alveolar epithelium. They stressed the generalized congestion, the hemorrhage into the pulmonary parenchyma and the albuminous, rich, serous exudate that occupies the foreground in the picture of the acute disease. These features were observed in patients who had suffered from intense cyanosis, dyspnea and pulmonary hemorrhage. The acute necrosis, which involves first the epithelium of the trachea, bronchi and bronchioles, and which may extend beyond the epithelium into the walls of these structures or may even destroy *en masse* the walls of the alveoli, causes a lesion which they believed occurred characteristically in influenza and could not be brought about by other types of acute pulmonary infection. They did believe that the action of various war gases on the lungs produced effects similar to those seen in influenza. Similar changes after inhalation of war gases were noted by a number of German workers, as is shown in the monograph of Kuczynski and Wolff.[7] Aschoff [8] also described the appearance of the alveolar walls after inhalation of war gas and spoke of swelling (imbibition) and homogeneizing of the alveolar walls due to chemical toxic changes.

Brannon and Goodpasture,[9] in 1924, suggested the possibility that the hyaline membrane was the result of damage caused by a circulating toxin which occurred in cases of severe influenza, and which caused mild injury of variable degree to the capillary bed of the lungs. They believed that this injury to the pulmonary capillaries permitted an exudation into the alveolar spaces of fibrinogen-containing serum, and that from this exudate fibrin would quickly form, adhere to the alveolar walls, and become fused, thereby forming a "membrane."

Wolbach,[10] and later Opie, Blake, Small and Rivers,[11] offered the suggestion that the hyaline membrane was related to the action of air on some of the body fluids or exudates. Wolbach described the membrane as being closely applied to the walls of the alveoli and alveolar ducts, and as sometimes apparently replacing them, but in other areas as being actually separated from these walls by desquamating epithelial cells or by red cells and leukocytes. He believed that the formation of the membrane was not dependent on the presence of necrotic alveolar walls. Wolbach concluded that the arrangement and outline of this hyaline material were determined by its contact with air, which must be under some tension.

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6. Winternitz, M. C.: The Pathology of War Gas Poisoning, New Haven, Conn., Yale University Press, 1920. Winternitz.[1] Winternitz, M. C.; Smith, G. H., and McNamara, F. P.: J. Exper. Med. **32**:199, 205 and 211, 1920.

7. Kuczynski, M. H., and Wolff, E. K.: Ergebn. d. allg. Path. u. path. Anat. **19**:947, 1921.

8. Aschoff, L., quoted by Kuczynski and Wolff.[7]

9. Brannon, D., and Goodpasture, E. W.: Arch. Int. Med. **34**:739, 1924.

10. (*a*) Wolbach, S. B.: Bull. Johns Hopkins Hosp. **30**:104, 1919. (*b*) Wolbach, S. B., and Frothingham, C.: Arch. Int. Med. **32**:571, 1923.

11. Opie, E. L.; Blake, F. S.; Small, J. C., and Rivers, T. M.: Epidemic Respiratory Disease, the Pneumonias and Other Infections of the Respiratory Tract Accompanying Influenza and Measles, St. Louis, C. V. Mosby Company, 1921.

MATERIAL AND PROBLEMS

A number of pertinent questions are raised by this lack of agreement in the literature regarding the histogenesis of the membrane. These questions shape themselves as follows:

1. Is the hyaline membrane pathognomonic of influenzal pneumonia? Is it the "virus lesion" of influenza?
2. What is the composition of the membrane?
3. What is the mechanism of its formation?

SPECIFICITY OF THE HYALINE MEMBRANE FOR INFLUENZA

The hyaline membrane has been generally regarded as pathognomonic of influenza, and it has been described as the distinctive lesion caused by the virus of influenza. In 1924, Brannon and Goodpasture [9] reported two instances of the occurrence of hyaline membranes in the absence of any association with influenza. Johnson,[12] in 1923, quoted a personal communication from Professor Hayashi of Japan to the effect that hyaline membranes were observed in pneumonic plague.

In a recent communication, Farber and Sweet [13] called particular attention to the occurrence of similar membranes in the lungs of new-born infants with a birth history suggesting intra-uterine asphyxia with aspiration of amniotic sac contents. The term vernix membrane was applied to these structures. These membranes are indistinguishable in appearance, position and ordinary staining reactions from the hyaline membranes of influenza. Since our last report, we have observed vernix membranes in the lungs of over fifty new-born infants.

During the past two years, we have seen typical hyaline membranes in the lungs of twenty infants and young children, varying in age from 3 months to 4 years, whose deaths were caused by pneumonia due to infection with Streptococcus hemolyticus. In addition, hyaline membranes were observed in the lungs of a young child who died of acute tuberculous pneumonia, a young adult who died of streptococcic bronchopneumonia, and a man of 42 whose illness ran the typical course of lobar pneumonia. In the last case, numerous membranes were found in a less involved portion of the lung (figs. 2 and 3).

The membranes in all of these instances were identical in appearance and staining reactions with those seen in influenzal pneumonia. There was no clinical or pathologic evidence of influenza in any of these cases.

It is evident from the occurrence of typical hyaline membranes in such a variety of conditions in the absence of any suggestion of influenza

12. Johnson, W. C.: Proc. New York Path. Soc. **23**:138, 1923.
13. Farber, S., and Sweet, L. K.: Am. J. Dis. Child. **42**:1372, 1931.

that the hyaline membrane is not pathognomonic of influenza. There remains, however, the possibility that the membrane may represent the distinctive lesion of the virus of influenza, a lesion that may be present only incidentally in the various instances that we have cited. This question we shall attempt to answer later in this study.

THE COMPOSITION OF THE HYALINE MEMBRANE

The typical membrane consists of a mass of homogeneous amorphous material, in which cellular débris and bacteria can occasionally be found.

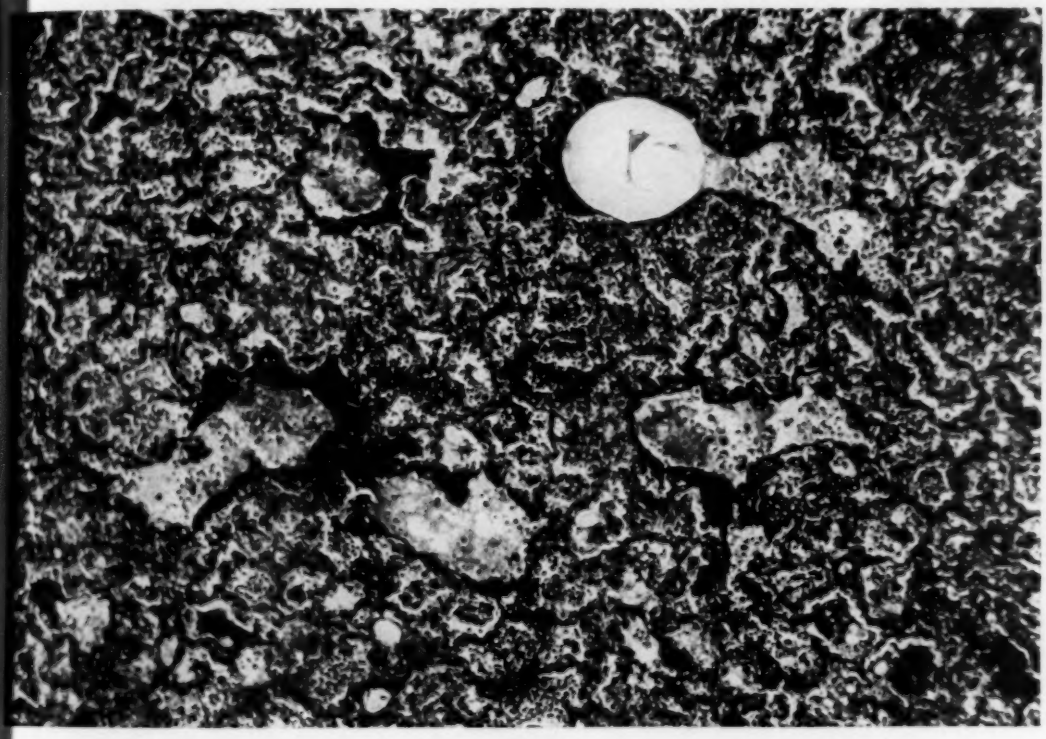

Fig. 2.—Photomicrograph of lung from an infant who died of acute streptococcic bronchopneumonia. Note membranes and bubble of entrapped air. Aniline blue; reduced from a magnification of × 104.

Both in cases of influenza and in those of pneumonia that we studied, the appearance of the material in the membrane is that of fused, resolving exudate consisting of necrotic mononuclear cells, leukocytes, erythrocytes, altered fibrin and serum, and débris from the alveolar walls, when necrosis of these walls is present. The material in the membrane can best be compared to the exudate in lobar pneumonia during the stage of resolution when autolysis of the exudate is taking place and cellular

detail can no longer be identified. Under these circumstances, former staining reactions are lost, and the necrotic materials stain deeply with eosin. A similar change characterizes the appearance of necrotic débris in an area of tuberculous caseation. When viable cells are present in the membrane, organization is probably taking place, for, as Wolbach [10b] showed, during repair there is invasion of the membrane by leukocytes and phagocytes. Eventually organization with connective tissue takes place in the membrane, as is well shown in the illustration in his paper.

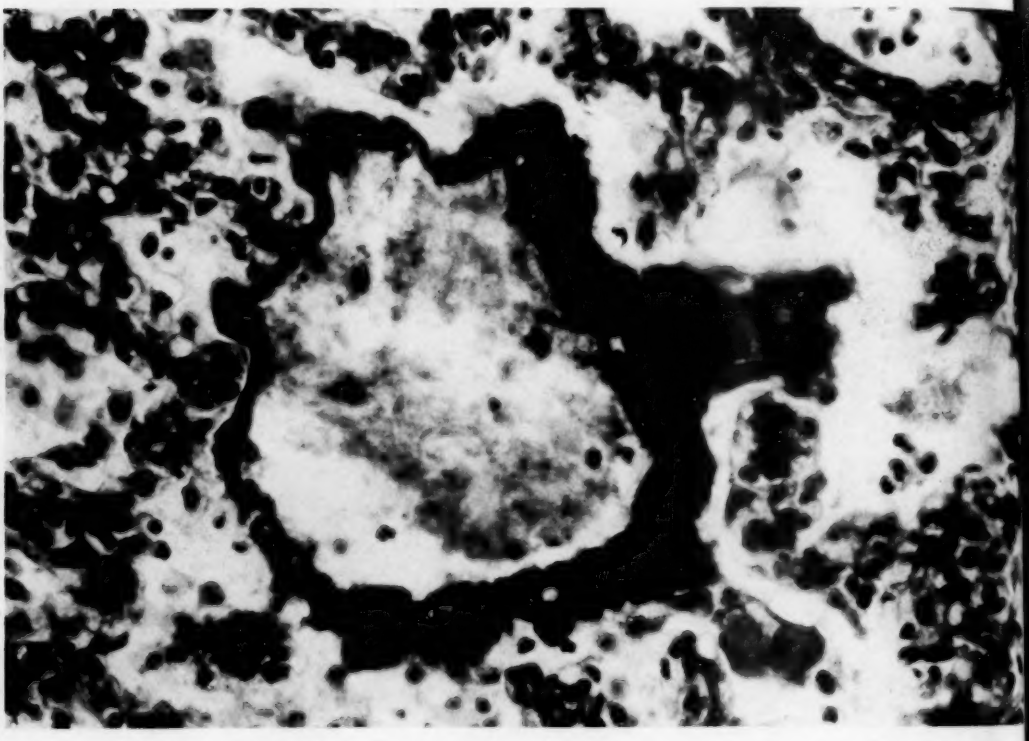

Fig. 3.—Photomicrograph of lung; a high power magnification of a detail of figure *2*; reduced from a magnification of × 500.

The membrane found in the lungs of new-born infants (vernix membrane) consists of amorphous material, embedded in which can be found cornified epithelial cells. It was shown [13] that this type of membrane, identical in appearance and staining reactions with the hyaline membrane, consists of aspirated amniotic sac contents. The bulk of this membrane is composed of vernix caseosa. There is no evidence of necrosis in association with the vernix membrane.

Differential stains (phosphotungstic acid hematoxylin) failed to show fibrin in any of the membranes in this study. In a few instances, in

the cases of pneumonia, in the presence of a fresh exudate, occasional strands of fibrin could be seen superimposed on, or pressed against, the membrane. The fresh deposits of fibrin could easily be distinguished from the main body of the membrane by the differential stain employed. In alveoli bordering those containing membranes, occasional small networks of fibrin could be identified readily in the phosphotungstic acid hematoxylin stain. However, there is no doubt that altered or digested fibrin may be one of the components of the membrane in the cases of

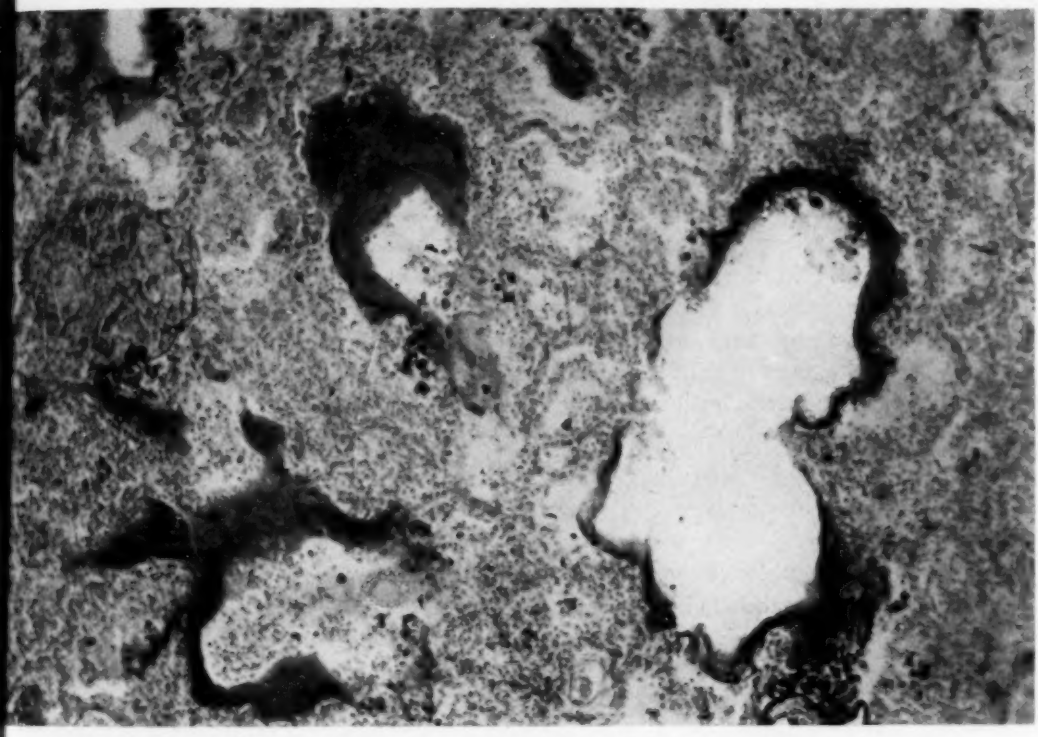

Fig. 4.—Photomicrograph of lung from the same patient as in figure 1. Note the large amounts of fat in the membrane. Scarlet red; reduced from a magnification of × 104.

pneumonia, despite the failure of staining reactions, for as Brannon and Goodpasture pointed out, the hyaline fibrin of a diphtheritic exudate does not retain the staining reactions of fibrin.

Scharlach R stains after formaldehyde fixation revealed a surprising finding: In the lungs of an adult who had died of acute, or fulminating, influenzal pneumonia, and in those of the majority of the young children who died of streptococcic pneumonia whom we examined, large amounts of fat were present in the form of both large and fine droplets, which

had coalesced to form broad, continuous, homogeneous bands of red-staining material, duplicating perfectly the outline of the membrane as seen in ordinary stains. Scattered throughout other portions of the sections there could be found small droplets of fat, usually within phagocytes. In other instances, fat stains were not so striking. However, even in cases in which only slight amounts of fat were present, it existed in the form of fine droplets within phagocytes, comparable in amount to that which can be found in any pneumonic lung when a considerable amount of exudate is present (fig. 4).

Fat in large amounts is constantly present in the vernix asphyxial membranes, representing here the high fat content of the aspirated vernix caseosa.

To summarize: The hyaline membrane in influenzal pneumonia, the membranes associated with the various types of pneumonia in our series, and the vernix membranes have the same staining reactions. They vary from pink to red with hematoxylin and eosin, and from salmon pink to red with the phosphotungstic acid hematoxylin stain. There is some variability in the amount of fat in the membranes associated with pneumonia. The vernix membranes can be differentiated from all other hyaline membranes by the cornified epithelial cells from the amniotic sac contents embedded in the vernix membrane. These can usually be identified in the ordinary stains. The Gram stain followed by acid alcohol decolorization has proved of use in doubtful cases. Special stains failed to show unaltered fibrin in the membrane.

MECHANISM OF THE FORMATION OF THE MEMBRANE

The membranes that we have studied varied in size and appearance from thin strands to broad, sweeping bands of eosin-staining amorphous material, in which cellular débris was frequently embedded. Often a membrane filled more than half of the lumen of a bronchiole or an alveolar duct, usually becoming thinner as it followed the walls of the finer ramifications of an alveolar duct. Characteristically, it sealed off whole groups of pulmonary structures, most often surrounding a bubble of entrapped air or a collection of serum. In some cases, the membranes were so numerous and their continuity so preserved that an efficient barrier to the passage of air must have been presented terminally.

One of the most frequent observations in the cases of pneumonia was that of masses of amorphous eosin-staining material free in the lumens of bronchioles and alveolar ducts. These masses of amorphous material were similar in appearance and staining reactions to the material in the hyaline membrane. Sometimes they were spread thickly around small bubbles of entrapped air in the centers of alveolar spaces. These masses varied greatly in size and shape. This finding recalls

exactly that of masses of vernix caseosa in similar situations in the lungs of new-born infants.

Typical membranes, formed at some distance from the alveolar walls, and separated from them by serum or red cells, were frequently encountered. Necrosis of alveolar walls was present in a number of the cases of streptococcic pneumonia and in the case of influenzal pneumonia. Although membranes frequently were seen adjacent to necrotic alveolar walls in these cases, we have repeatedly observed membranes lining intact walls with perfect preservation of the epithelium. The vernix membrane occurred most often in cases in which pneumonia was lacking and in which no evidence of necrosis of the alveolar walls could be found.

In the series of pneumonic lungs of various types in which we found typical hyaline membranes, the absence of large amounts of exudate in areas where membranes were numerous was at first striking. In regions where membranes were lacking, the alveoli were usually completely filled with an acute inflammatory exudate consisting of leukocytes, erythrocytes and fibrin in a state of good preservation. The leukocytes in such areas stained clearly, and the exudate appeared recent in origin. Where membranes were numerous, exudate with good cellular detail was absent, except in rare instances when a superimposed acute exudate was found. These different pictures in the same person point to a variation in the age of the inflammatory processes and explain the apparent aplastic appearance of the exudate in areas where membranes were numerous. In such areas, the pathologic process had advanced to a point where autolysis of the exudate was taking place, and cellular detail could no longer be identified. The characteristic eosin-staining appearance and the amorphous, homogeneous consistency of the components of the membrane in the cases of pneumonia depend on the presence of necrotic débris and of old, partially autolysed exudate.

Wolbach [10b] described in two instances typical hyaline membranes surrounding bubbles of air in the areolar tissues of the mediastinum, which was the site of emphysema and also of pneumococcic mediastinitis. On one occasion we observed typical membranes outside the lung, in the mediastinal areolar tissues of a young child who had died of a descending infection of the upper respiratory tract by S. hemolyticus. A tracheotomy had been performed, and air had dissected into the mediastinum, which had participated in the streptococcic infection. Lining the emphysematous areas were membranes that had the same appearance and staining reactions as those in the lungs (fig. 5).

The various theories regarding the formation of the membrane have already been outlined. The hypothesis of Brannon and Goodpasture rests on the existence of an injury of the capillary bed with an outflow

of fibrinogen-containing serum. Winternitz and his associates, reporting on their experiments with war gas poisoning and insufflation of hydrochloric acid, described, in addition to the necrosis of the alveolar walls, an albuminous, rich, serous exudate that was prominent in acute disease and thick, colloid-like material within the alveoli. Oberndorfer [14]

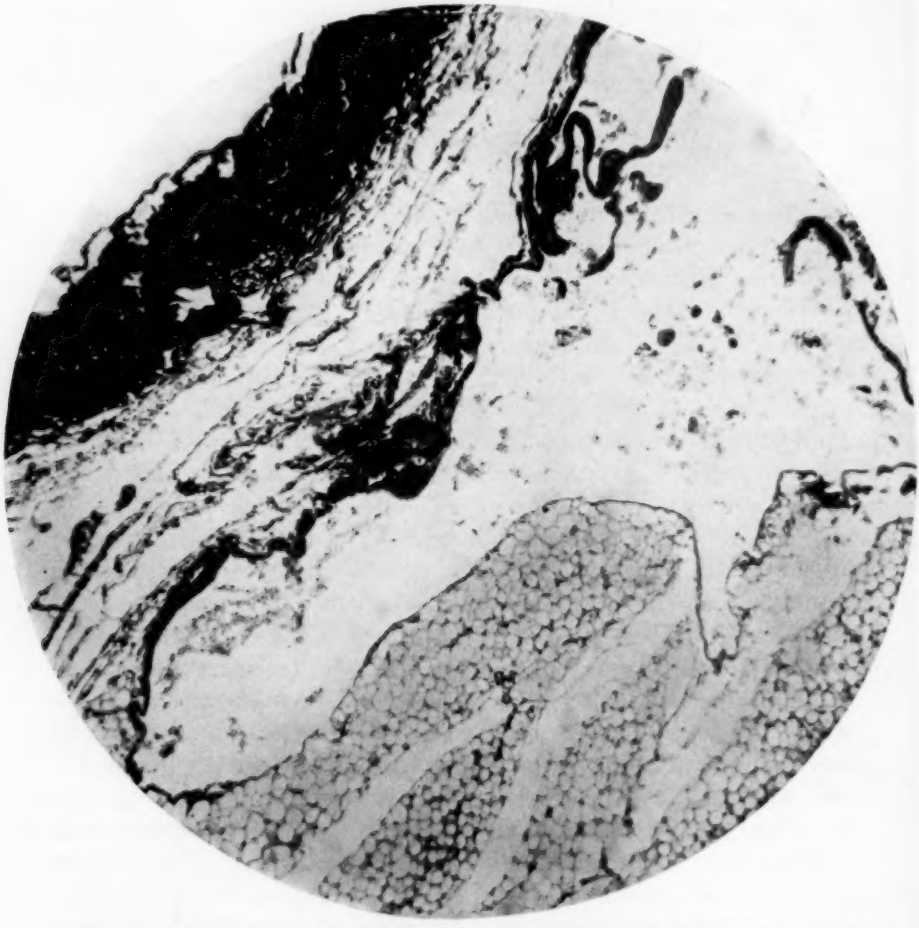

Fig. 5.—Photomicrograph of mediastinum showing interstitial emphysema, from a person with streptococcic mediastinitis. Note the space occupied by air lined by typical hyaline membrane. Aniline blue; reduced from a magnification of × 68.

emphasized the degree of vascular damage in influenza, describing a primary damage resulting in increased capillary permeability. There is abundant mention of such damage in the literature. According to Luksch,[3] Stoerck and Epstein found changes in the elastica interna and

14. Oberndorfer, S.: München. med. Wchnschr. **65**:811, 1918.

muscularis of the medium-sized arteries, with areas of necrosis in the muscularis. Thrombi have been noted by numerous observers and have been regarded by Leichtenstern [15] as primary in a certain number of cases of influenza. The large collections of serum in the lungs and the copious amounts of thin, serosanguineous exudate noted both clinically and pathologically in influenzal pneumonia indicate vascular damage. However, such damage is not peculiar to influenza or to inhalation of war gases. Vascular damage due to a variety of causes will bring about similar pictures, as, for example, in streptococcic pneumonia. Oswald showed (according to Wells [16]) that in inflammation the permeability of the vessels for protein becomes specifically altered, so that not only the less viscous albumin and pseudoglobulin pass through their walls, but also the more viscous euglobulin and fibrinogen. Fluid may collect in alveolar spaces owing to other causes. Increased blood pressure, particularly in the presence of damage to the vascular bed, or obstruction to the lymphatic drainage, either by thrombotic plugging of the lymphatics or by pressure on the outside, may play a part.

Damage to the vascular bed undoubtedly accounts for a great part of the exudate in the alveolar spaces in influenza and also in streptococcic pneumonia. Although this exudate contributes later to the composition of the membrane, it is not in itself an adequate explanation for the actual formation of the membrane.

There remains to be considered the theory that the membrane represents a hyalinization of necrotic alveolar walls, similar to that after war gas poisoning or after insufflation of hydrochloric acid. There are a few objections to this theory. As we have stated, we repeatedly observed typical hyaline membranes lying against healthy alveolar walls, and we also noted membrane formation at some distance from alveolar walls. The vernix membranes are usually found lining structures in which necrosis cannot be demonstrated. That the membrane is not related specifically to degenerated epithelium is shown by the two cases reported by Wolbach and by our own similar case in which typical membranes were found in the presence of emphysema and mediastinitis in the tissues of the mediastinum, where no epithelium existed. Necrosis of the alveolar walls, when present, probably adds to the necrotic material taking part in the composition of the membrane. However, an explanation for the occurrence of the hyaline membrane must be sought elsewhere than in a specific effect of some irritant on the alveolar walls. It is interesting to recall that the vernix membrane was first described as an "influenza-like" lesion, and an attempt was made to relate the

15. Leichtenstern, quoted by Luksch.[3]

16. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925.

membrane to the aspiration of some irritant, such as lysol, from the vaginal contents during birth. However, a number of our most striking examples of the vernix membrane were found in the lungs of infants who had been delivered by cesarean section where this possibility did not exist.

Any explanation of the formation of the membrane must take into consideration not only the membrane seen in influenzal pneumonia, but also that found in the various types of pneumonia that we have described and the membranes occurring after aspiration of amniotic sac contents. In general, they all have the same appearance and staining reactions, and except for a few details in the composition of the vernix membrane, they are indistinguishable from one another.

The outstanding clinical and pathologic features of these cases of influenzal and streptococcic pneumonia are marked dyspnea (with emphysema) in addition to the presence of a large amount of semifluid material in the air spaces. Similar features characterize the cases of aspiration of amniotic sac contents which we have described. The small and large masses of eosin-staining amorphous material found free in the alveolar spaces both in the persons who died of pneumonia and in the new-born infants whom we studied have been described. These masses we regard as early stages in the formation of the membrane before the material has been pressed against the alveolar walls. From a study of our material, with particular reference to these free masses, we believe that a sequence of events leading to the formation of the membrane can be followed. This sequence can be traced from the coalescence of small masses of amorphous eosin-staining material, free in the alveolar ducts and later in the alveolar spaces, with dispersion toward the periphery to an ultimate close application of the material against the alveolar walls in characteristic membrane formation. This sequence is similar to that noted after aspiration of amniotic sac contents with formation of the vernix membrane.[13] The dispersion of the coalesced amorphous materials to the periphery, the characteristic picture of such substances surrounding bubbles of entrapped air, and the occurrence of typical membranes in the mediastinum in the presence of mediastinal emphysema and exudate all demonstrate a relationship of air to the formation of the membrane—a relationship emphasized by Wolbach[10] and later by Opie, Blake, Small and Rivers.[11]

In the light of our observations it has seemed that the necessary factors for the production of the characteristic hyaline membranes are: (1) the presence of material capable of taking the characteristic eosin stain, (2) air in the alveolar spaces, probably under greater than normal tension, (3) partial obstruction to the passage of the air by semifluid

material in the air passages and (4) dyspnea, which may be interpreted as violent inspiratory efforts in an attempt to force air by this obstruction.

We believe, then, that the position of the eosin-staining substance lying characteristically as a membrane along alveolar walls may be simply the result of the mechanical dispersion of this foreign material toward the periphery by air violently inspired. Further investigation of this mechanical distribution was undertaken.[17]

CONCLUSIONS

The hyaline membrane is not pathognomonic of influenzal pneumonia. Identical membranes are found in the lungs of persons with various types of pneumonia and in the lungs of new-born infants after aspiration of amniotic sac contents.

The membrane may contain large amounts of fat. Fibrin cannot be demonstrated in the membrane by special stains.

The formation of the membrane is dependent neither on necrosis of alveolar walls nor on vascular damage, although both these factors may contribute to the production of exudate, which may ultimately enter into the composition of the membrane.

Dyspnea is the outstanding symptom in patients in whose lungs membranes occur.

The position of the eosin-staining substance lying characteristically as a membrane along alveolar walls is simply the result of the mechanical dispersion of foreign material toward the periphery of the air sacs by air violently inspired. This material consists of autolysed exudate and necrotic débris in cases of influenzal and streptococcic pneumonia, and of vernix caseosa and cornified epithelial cells in instances following aspiration of amniotic sac contents.

17. Farber, S., and Wilson, J. L.: Arch. Path., this issue, page 450.

THE HYALINE MEMBRANE IN THE LUNGS

II. AN EXPERIMENTAL STUDY

SIDNEY FARBER, M.D.

AND

JAMES L. WILSON, M.D.

BOSTON

In a study [1] of the formation and significance of the hyaline membrane in the lungs, frequently described in influenzal pneumonia, and considered by many pathognomonic of that disease, we concluded that the membrane was not specific for influenza, but was probably produced by the mechanical forcing of air into alveoli through material which took the eosin stain and which was composed either of necrotic débris and autolysed exudate or of aspirated amniotic sac contents. The membrane formation we considered to be a result of foreign material being pressed against the alveolar walls by entrapped air, but having no essential causal relationship to the alveolar walls.

Since the staining reaction was explained by the character of the foreign material in the air spaces, which was not necessarily essential to the formation of the membrane, attention could be centered on the physical mechanism involved. It was determined, therefore, to ascertain in other instances in which similar mechanical conditions in the air passages obtained, whether there were comparable membrane-like formations lining the alveolar walls, not necessarily with the same staining reaction as the typical hyaline membrane. An effort was also made to reproduce experimentally the formation of such membranes, and to ascertain the origin of the fat frequently found in the hyaline membrane.

A consistent clinical feature of patients in whose lungs the characteristic hyaline membrane was found was marked dyspnea, apparently resulting from the necessity of a forceful inspiration of air by and through obstructing exudate. There were frequently such large amounts of fluid in the air passages of patients dying of influenzal pneumonia that Wolbach [2] remarked: "The patient is virtually blow-

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1. Farber, Sidney, and Wilson, J. L.: Arch. Path., this issue, page 437.

2. Wolbach, S. B.: Bull. Johns Hopkins Hosp. **30**:104, 1919.

ing bubbles in his own lung." We have seen similar situations in the following conditions:

1. Poliomyelitis. In many cases of poliomyelitis with respiratory paralysis or with pharyngeal paralysis, the filling of the lungs with exudate or with aspirated mucus and vomitus is common. We have studied the lungs of six such patients, who died while artificial respiration was being maintained in a Drinker respirator. It was understandable that in a final effort to save their lives these patients were subjected to particularly forceful inspiratory efforts produced by the machine—in most cases, a procedure maintained probably for several minutes after the heart had stopped. Under such conditions, air was forced into alveoli filled with variable quantities of serum or foreign materials. In patients who were similarly affected and who were not treated in the Drinker respirator, a similar result but to a lesser extent was brought about by the patient's own efforts at respiration. At autopsy, the lungs were heavy and voluminous and contained large quantities of serum. Microscopically, the alveoli, alveolar ducts and bronchioles were distended and filled with serum. Numerous instances were observed of large air bubbles surrounded by serum which had been pressed against alveolar walls in membrane formation. Often artificial alveolar boundaries were thus formed, and it was sometimes difficult to recognize the true alveolar walls. This always occurred in greatly distended air spaces, and the appearance of large air bubbles entrapped in the serum which had been pressed against the alveolar walls was striking. This picture was not found in areas where consolidation had taken place (fig. 1).

2. Streptococcic bronchopneumonia. An infant, 3 months of age, died following acute streptococcic bronchopneumonia. A pulmotor had been applied by an "emergency crew" when the child apparently was dead. At autopsy, the lungs were tremendously distended, and the alveoli were filled with serum and red cells. A picture similar to that seen in the cases of poliomyelitis was observed. Membranes composed of serum and surrounding entrapped air lined the walls of the greatly distended spaces. In other areas, the alveoli were packed with large amounts of serum and small numbers of red cells (fig. 2).

3. Influenzal pneumonia. An identical picture was seen in a case of influenzal pneumonia in an adult. In a portion of the lung which was filled with serum, again membrane-like formations composed of serum could be frequently found lining the alveolar walls and surrounding bubbles of entrapped air.

4. Lobar pneumonia due to Friedländer's bacillus. Membranes surrounding bubbles of air were noted in the lungs of an adult who had died of Friedländer's type of lobar pneumonia. In the more emphysematous portions of the lung, numerous membranes composed of serum and occasional leukocytes could be found. Frequently such membrane formation was noted some distance from alveolar walls, and occasionally three or more small membranes surrounding bubbles of air could be found in one distended alveolar duct.

5. Acute infection of the upper respiratory tract. In the lungs of five infants who had died of an acute infection of the upper respiratory tract with Streptococcus hemolyticus, membranes composed of serum, red cells and sometimes large numbers of leukocytes could be found lining the walls of air spaces and, in a few instances, also pressed against the mucosal surfaces of bronchioles. On a few occasions, in these cases, membranes composed of a loose cellular exudate, poor in fibrin, were observed.

6. Bronchial obstruction. An infant died following partial plugging of the bronchi with aspirated milk. There was partial obstruction to the passage of air,

and violent dyspnea terminating in asphyxia occurred. Microscopically, the essential features were overdistention of the air spaces, the presence of serum in the alveoli, and the formation of membranes composed of serum and a few red cells and applied to the alveolar walls. As was shown by fat stains, little milk had found its way into the alveoli.

7. Cardiac failure. We have observed similar formations in the lungs of a number of patients who had died of cardiac failure after chronic passive congestion of the lungs and increasing dypnea. Again the picture described was noted in numerous areas of the lungs. Membranes composed of serum and occasional red

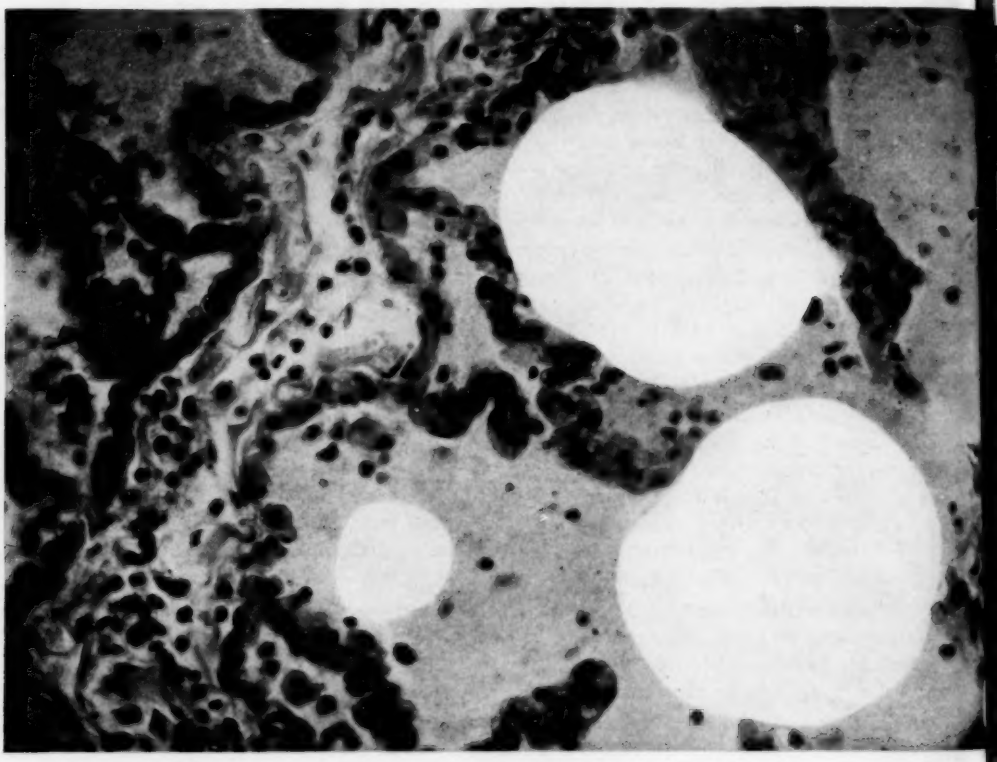

Fig. 1.—Photomicrograph of lung from a young child who died of poliomyelitis. Note the distention of the air spaces and the large amounts of serum in membrane formation surrounding entrapped bubbles of air. Hematoxylin and eosin; × 400.

cells, and usually formed at some distance from alveolar walls, could be found with ease.

In all of these instances, marked dyspnea and forceful inspiratory efforts were prominent clinical features. Air was presumably brought into the lungs under an intra-alveolar pressure relatively greater than normal becauses of the combination of forceful inspiration and partial obstruction. Obstruction to the passage of air was always present, owing to partial plugging of the bronchi by foreign material. The consequence of air being thus forced into and through various types

of obstructing material was the formation of membranes surrounding bubbles of entrapped air. The membranes were formed either against or at some distance from the alveolar walls. The staining reaction of the membrane in each case depended on the substances present in the air spaces, serum, red cells, leukocytes, etc. These membranes were identical in shape, position and mechanism of formation with the vernix membrane and the typical hyaline membrane of influenzal and streptococcic pneumonia.

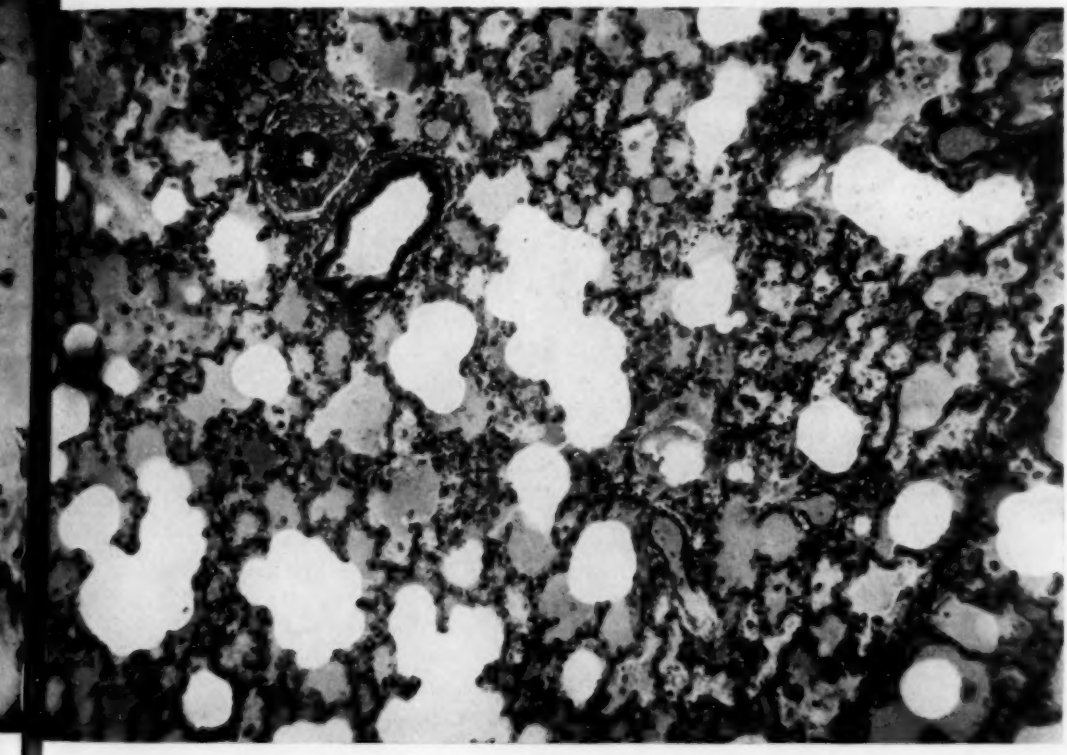

Fig. 2.—Photomicrograph of lung from a 3 months old infant who died of acute streptococcic pneumonia. A pulmotor was applied in an attempt to prolong the infant's life. Note the distended air spaces and the collections of serum in membrane formation surrounding the entrapped air. Hemaxtoylin and eosin; reduced from a magnification of × 112.

EXPERIMENTAL PRODUCTION OF MEMBRANES

As has been mentioned before, the two factors that seem necessary for the formation of these membrane-like structures in the alveoli are the presence of foreign fluid matter in the air passages and dyspnea with forceful inspiratory efforts. Reproduction of these conditions experimentally without the production of bacterial inflammation was

undertaken in an effort to demonstrate the mechanical basis for this histologic picture. All animals used in these experiments were anesthetized by intraperitoneal injections of either amytal or paraldehyde. The experimental procedures were as follows:

Asphyxia With and Without Dyspnea.—A series of rabbits was placed in small, air-tight glass containers and allowed to remain until death from asphyxia occurred. The jars were of such a size that two and one-half hours elapsed before the oxygen was sufficiently used up to produce death. Marked dyspnea resulting from the accumulation of carbon dioxide was present for much of the time.

A second series of animals was allowed to die in a similar manner, except for the constant removal of the carbon dioxide by soda lime. In these animals there occurred only a small amount of terminal dyspnea. At autopsy, the lungs of the first series of rabbits, which died with evidence of marked dyspnea, were dark salmon pink externally. On section, the cut surfaces showed marked congestion, and large amounts of blood flowed freely from the larger vessels. Serum could be readily expressed from the parenchyma on pressure. Microscopically, the blood vessels showed marked congestion, and the alveoli were definitely distended and contained varying amounts of serum, often pressed against alveolar walls in membrane-like formation. The lungs of the second group of rabbits, which died without marked dyspnea, showed no distention of the alveolar spaces and only small amounts of serum in these spaces. No membrane formation had occurred.

Aspiration of Ink with Resulting Dyspnea.—A number of young rats were immersed in a solution of 10 per cent india ink for from one to two minutes. They were then removed and permitted to breath with marked dyspnea for a few minutes before they were killed. At autopsy, the ink could be seen distributed throughout all lobes of both lungs. Microscopically, the alveoli contained large amounts of the ink solution, sometimes gathered in small patches without definite shape, free in the air spaces, but more often forming complete rings around air spaces, lining the walls and often sealing off groups of alveoli. These membrane-like formations were usually not very wide and were characteristically formed around entrapped bubbles of air. The india ink membranes were an exact duplication of the hyaline membrane of influenza in shape, position and general outline, and differed only in staining reaction (fig. 3).

Aspiration of Foreign Material During Artificial Respiration.—In order to produce even more excessive respiratory movements in the presence of obstructing fluid matter in the air passages than an animal would produce by itself, a small improvised Drinker respirator was utilized. The animals were placed in the respirator after anesthesia and subjected to violent artificial respiration (vacuum up to 30 cm. of water pressure). While artificial respiration was maintained, horse serum, india ink and various types of purulent material were injected into the tracheas of these animals. Respirations were maintained in the Drinker apparatus for varying intervals of time, and then the animals were killed. Cats, rabbits and puppies were used in these experiments. In every case, the material, could be found in the alveolar spaces. The foreign matter was usually all lobes of both lungs. Usually collections of serum, in addition to the injected material, could be found in the alveolar spaces. The foreign matter was usually widely dispersed throughout all the alveoli, sometimes collecting in small patches, but more often forming typical membrane-like structures against the alveolar walls. The most striking pictures were obtained after the injection of india ink, because

of the outstanding color of the ink. However, in all cases, the the same type of formation as regards shape and position could be found.

Insufflation of Hydrochloric Acid, with Vascular Damage and Dyspnea.—Several rabbits were subjected to insufflation of hydrochloric acid in imitation of the experiments of Winternitz and his co-workers;[3] 7 cc. of a 1 per cent solution of concentrated hydrochloric acid in physiologic solution of sodium chloride was injected intratracheally. Immediately, the respirations became of a noisy, obstructive type, and diffuse fine râles could be heard over the lungs with the stethoscope. Marked dyspnea was brought about. Frothy, serosanguineous fluid flowed from

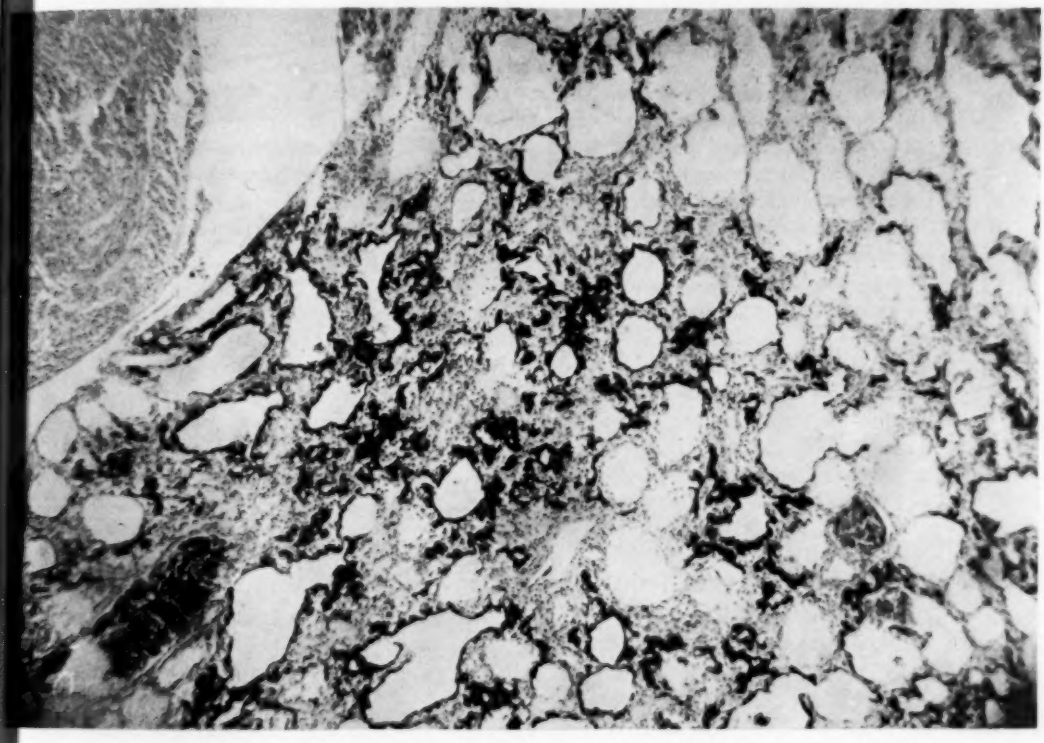

Fig. 3.—Photomicrograph of lung from a young rat that had been immersed in india ink. Note the membranes composed of ink outlining the air spaces and surrounding the entrapped air. Hematoxylin and eosin; reduced from a magnification of × 104.

the mouth during the last few minutes of life. At autopsy, the mucosal surface of the trachea was reddened and covered by foamy, serosanguineous fluid exudate. The lungs showed patches of consolidation, and numerous hemorrhagic areas of varying size and shape could be seen beneath the pleura. On section, the cut surfaces were edematous and hemorrhagic. Microscopically, the main features were edema and hemorrhage into the alveoli. The alveolar spaces were filled with large

3. Winternitz, M. C.; Smith, G. H., and McNamara, F. P.: J. Exper. Med. **32**:199, 1920.

amounts of serum and smaller amounts of red cells. The blood vessels showed marked congestion and early thrombi. In scattered areas, serum was packed against the alveolar walls in membrane formation. In two areas, membranes reminiscent of the hyaline membrane of influenza were seen lining alveolar walls, which showed early necrosis. The membranes consisted of loose fibrin, serum and a small amount of necrotic débris. Distention of the alveolar spaces was a marked feature. The vascular lesions and the marked amounts of serum and blood in the alveoli overshadowed the comparatively small amount of necrosis of alveolar walls in animals treated by insufflation of hydrochloric acid.

Experiments Showing Exudate as an Essential Factor.—Several experiments were devised to show the necessity for the presence of an exudate as well as of air under some pressure in order to produce the membrane. A cat was overventilated to such a degree that mediastinal emphysema resulted. However, no exudate was present in the mediastinum, and on section, although mediastinal emphysema was demonstrated, there was no membrane formation. In contrast to this situation, air and purulent material obtained from other sources were both forced into the areolar tissues beneath the skin of a rabbit. On section, the air bubbles were surrounded by the fibrinopurulent exudate that had been injected. Typical membrane-like formations occurred in this case, of characteristic hyaline appearance.

Experiment Further Demonstrating Mechanical Nature of Formation of Membrane.—To ascertain whether the living animal was necessary for the formation of the membrane, two rabbits were killed, and india ink was injected intratracheally when the animals were in the Drinker respirator. Artificial respiration under increased pressure was then instituted. Microscopically, a picture just as striking as that seen after insufflation of india ink in the living animal was found. Ink membranes in characteristic position and outline could be found in large numbers throughout the lungs.

SOURCE OF FAT IN MEMBRANES

A number of experiments were designed to ascertain, if possible, the origin of the fat found in the membranes associated with certain of the cases of influenzal and streptococcic pneumonia. Two possibilities presented themselves. The fat might come directly from the blood stream into the alveolar spaces and so be incorporated in the membrane, or, as the result of autolysis, fat might be liberated from the exudate.

Experiment to Determine Whether Fat Could Be Drawn from the Blood Stream Under Varying Conditions.—Puppies, rabbits and rats were placed in the Drinker respirator and subjected to prolonged overventilation with varying degrees of pressure. In all cases there occurred marked distention of alveolar ducts and spaces with occasional rupture of alveolar walls. Serum and small collections of red cells, usually pressed against the walls of the air spaces, could be found. Fat stains (scharlach R after formaldehyde fixation) failed to reveal the presence of fat in the air spaces in any of the animals treated in this manner.

Experiment to Ascertain Whether Fat Could Be Brought from the Blood Stream into the Alveolar Spaces When the Blood Was Rich in Fat.—Four cats were fed heavy cream at varying intervals with the hope of temporarily increasing the fat content of the blood stream. Procedures similar to those just described were then carried out, following which the animals were killed. The lungs of these

cats showed emphysema, overdistention of the air spaces and small amounts of serum in the alveoli, usually pressed against alveolar walls. Globules of fat were present in the blood vessels of the lungs or in the peribronchiolar lymphatics, greatly in excess of the amounts usually seen. However, no fat could be demonstrated in the alveolar spaces.

Other Experiments in Which the Source of Fat Was Studied.—In the experiments in which horse serum was injected into the trachea and the animal then subjected to violent respiratory movement, no fat could be demonstrated in the resulting membranes. Staining for fat was done on the lungs of ali the animals subjected to any of the experimental procedures mentioned in foregoing paragraphs, and in no case could fat be demonstrated in the alveolar spaces. With death caused by overventilation, immersion followed by dyspnea, or asphyxia accompanied by hyperpnea and dyspnea or without dyspnea, stains for fat always gave negative results. After the insufflation of various substances, fat-free in themselves, similar negative results prevailed.

Evidence That Fat Is from Exudate.—The only other explanation of the presence of fat in the membranes in certain of the cases of streptococcic and influenzal pneumonia must depend on the production of fat from the purulent exudate in the lungs. There is abundant evidence for this supposition. In 1,000 parts of dried pus cells, there are 75 parts of fat and like amounts of lecithin and cholesterol. In addition, pus-containing serum shows approximately 1.2 per cent fat, cholesterol and lecithin, with fat representing 0.5 per cent (Wells [4]). Small amounts of fat are present in any pneumonic exudate (MacCallum [5]).

ARTIFICIAL PRODUCTION OF HYALINE MEMBRANE

The final problem was the artificial reproduction of an eosin-staining hyaline membrane. From histologic appearances and staining reactions it had been concluded that the eosin stain was due to the nature of the exudate and that of the débris included in the membrane and to the degree of autolysis which the exudate had undergone.

Fibrinopurulent exudate from a case of empyema was mixed with physiologic solution of sodium chloride and injected into the tracheas of one live and one dead rabbit, while the animals were subjected to forceful artificial respiration in the Drinker apparatus. Microscopically, the exudate was found in the alveolar spaces of both animals, often in membrane formation against alveolar walls. The membranes consisted of leukocytes and fibrin, and only in occasional small areas were they typically eosin-stained. Similar exudate was then allowed to stand in an incubator at 40 C. for two days, following which the material was injected as before into the tracheas of both *dead* and *live* rabbits, which were subjected to artificial respiration. Microscopically, the material was found scattered throughout the air spaces in all lobes of both lungs. Material was gathered, in part, in small patchy areas in the alveolar spaces and ducts. More often, however, the injected material was found pressed against alveolar walls in amorphous masses in which no cellular detail could be recognized. This material stained definitely

4. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925.

5. MacCallum, W. G.: Textbook of Pathology, ed 4, Philadelphia, W. B. Saunders Company, 1928.

pink to red in the hematoxylin and eosin stains, and by the phosphotungstic acid hematoxylin stain was negative for fibrin. The picture could not be distinguished from the hyaline membrane found so characteristically in influenzal pneumonia (figs. 4 and 5).

SUMMARY

Membrane-like structures lining alveolar walls and identical in position and shape but not in staining reaction with the so-called hyaline membrane of influenza were found, on histologic examination, in the lungs of patients dying from a variety of causes. The presence of

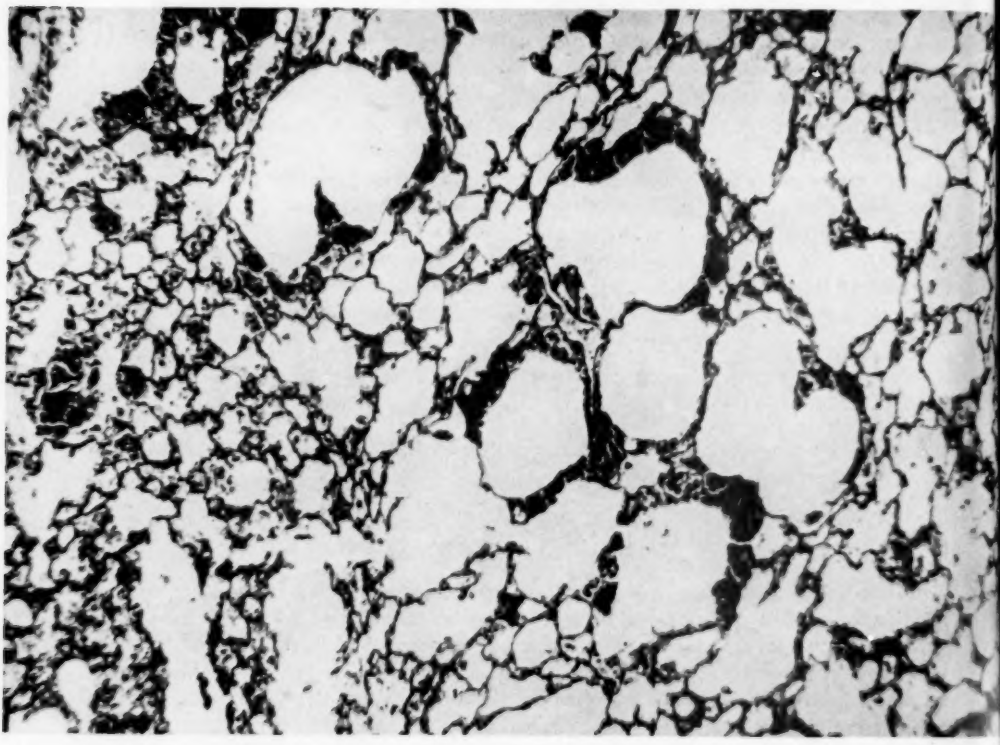

Fig. 4.—Photomicrograph of lung from a rabbit. Autolysed fibrinopurulent exudate was injected into the trachea after the animal had been killed. Artificial respiration was then carried out in the Drinker respirator. Note the position of the injected material in typical membrane formation. Aniline blue; reduced from a magnification of × 112.

fluid matter in the air passages, causing partial obstruction to the passage of air, and marked dyspnea characterized the deaths of all these patients.

The fat in the membranes in certain of the cases of influenzal and streptococcic pneumonia is best explained as fat liberated from the exudate as a result of autolysis. It was found impossible to draw fat

into the alveolar spaces from the blood stream by reproducing in a number of ways the important mechanical factors that are present in every case in which the membrane is found.

When animals were forced to breath an atmosphere of such low oxygen and high carbon dioxide that marked dyspnea leading to death occurred, the alveolar spaces were filled with varying amounts of serum frequently pressed by the inspired air into membrane formation against the alveolar walls. When the carbon dioxide was removed so that little

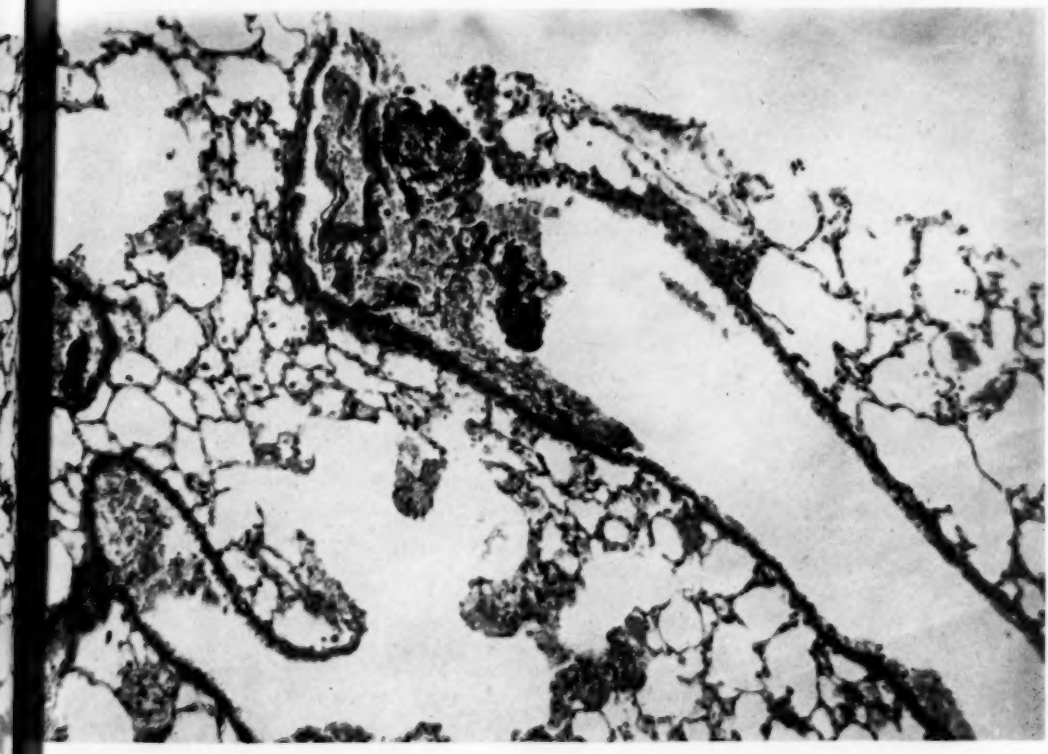

Fig. 5.—Photomicrograph of lung and bronchus from the rabbit described in the legend for figure 4. Note the hyaline, eosin-staining membrane near the wall of the bronchus. Hematoxylin and eosin; reduced from a magnification of × 125.

dyspnea occurred before death from anoxemia, serum was found in the alveoli but no membrane formation.

When a foreign substance, such as horse serum, india ink or fibrinopurulent exudate, was instilled into the trachea and vigorous artificial respiration (in a Drinker respirator) instituted, characteristic membranes formed of the material could be found lining the alveolar walls.

That the living animal is not necessary for the production of the membrane, and that only the correct mechanical conditions are of

importance, was shown by the production of membranes in the lungs of dead animals subjected to artificial respiration during the intratracheal injection of various foreign materials.

The absence of membranes in a mechanically produced mediastinal emphysema where no exudate was present, and the production of such membranes in artificial emphysema caused by the injection of both air and exudate into the subcutaneous tissues of an animal, stress the necessity of having both factors present for the formation of a membrane. These experiments recall the finding by Wolbach and by ourselves [1] of typical membranes in mediastinitis with emphysema.

The eosin-staining character of the typical membrane, as seen in influenzal and streptococcic pneumonia, was found to depend on the degree of autolysis of the exudate incorporated therein. It was possible by injecting suitable exudate into the tracheas of *dead* animals subjected to artificial respiration to produce typical eosin-staining membranes lining the walls of bronchioles and alveolar spaces.

THE BRAIN STEM IN PNEUMONIA

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There has been for many years a feeling that death in acute infections, particularly in pneumonia, is determined primarily by a failure of control of respiration and circulation by the central nervous system.[1] There is considerable physiologic evidence to support this theory.[2] No histologic studies of the effect of pneumonia on the nerve centers recognized as governing these functions have been found in the literature, although a few such studies are available on the effect of experimental anoxemia, electrocution and death by freezing.[3] The principal centers supposed to regulate these functions through both the somatic and the autonomic system are:

1. The motor nucleus of the trifacial nerve, the nucleus of the facial nerve, the hypoglossal nucleus, the nucleus ambiguus, the spinal accessory and anterior horn cells supplying somatic motor fibers, from large polyhedral cells well supplied with Nissl substance.

2. The vagus motor nucleus and sacral autonomic cells supplying principally autonomic motor fibers to smooth muscle, from cells of moderate size with somewhat less Nissl material.

3. The indefinitely located respiratory and vasomotor centers of association, lying supposedly in the pons and the medulla oblongata.

4. The central connections of the sympathetic system, thought to lie in the diencephalon (Bard[4]). They are not considered here, because these areas have not been studied. However, one recently studied brain, in which sections of the hypothalamus were made, showed areas of nerve cell degeneration in this region similar to that to be described for the more damaged portions of the brain stem.

From the Department of Medicine of the Medical School of the University of Pittsburgh and the Pathological Laboratories of Mercy Hospital.

1. Weiss, Soma: Ann. Int. Med. **5**:100, 1931. Janeway, T. C.: New York State J. Med. **85**:193, 1907. Crile, G. W.: J. A. M. A. **76**:149, 1921. Mott, Fred: Lancet **1**:519, 1921.

2. Keller, A. D.: Am. J. Physiol. **96**:59, 1931. Newburgh, L. H.; Means, J. H., and Porter, W. T.: J. Exper. Med. **24**:583, 1916. Porter, W. T.; Newburgh, L. H., and Newburgh, I.: Am. J. Physiol. **35**:1, 1914. Boothby, W. M., and Shamoff, V. N.: ibid. **37**:418, 1915-1916. Atchley, D. W.: J. A. M. A. **95**:385, 1930. Kastlin, G., and Maclachlan, W. W. G.: Ann. Int. Med. **4**:959, 1931.

3. Chornyak, John, and Sayers, R. R.: Pub. Health Rep. **46**:1523, 1931. Morrison, L. R.; Weeks, A., and Cobb, S.: J. Indust. Hyg. **12**:324 and 364, 1930. Urquhart, R. W. I.: ibid. **9**:140, 1927. Bender, L.: Arch. Neurol. & Psychiat. **20**:319, 1928.

4. Bard, P.: Arch. Neurol. & Psychiat. **22**:230, 1929.

The vasomotor center is supposed to lie somewhere in the medulla oblongata beneath the floor of the fourth ventricle. The respiratory center, according to Cajal (Ranson [5]), lies in the posterior commissure of the nucleus of the tractus solitarius, but opinions of Legalois and Flourens, Schiff and Girard, Mislavski, Gad and Marinesco, and Becterew (Tilney and Riley [6]) place it in the reticular gray matter of the pons and medulla. Lumsden,[7] in his physiologic experiments, divided the respiratory center into four parts, a regulatory center in the upper part of the pons, a center of inspiratory tone and an expiratory center in the upper part of the medulla near the level of the striae acousticae and a gasping center at the posterior limit of the fourth ventricle. The work of Lumsden will be discussed in detail in connection with the present work.

Function and failure of the respiratory mechanism are so closely linked with function and failure of the vasomotor mechanism that it seems likely, although unproved, that the anatomic centers of the control of these mechanisms lie in great proximity to each other. No attempt will be made to separate them, although it would appear that of the two, the more fundamental to life is the respiratory, since the vasomotor mechanism is developed secondarily, to meet the primary need for internal respiration in the multicellular organism.

MATERIALS AND METHODS

The present study deals with observations on the medullary and pontile centers in five cases of lobar pneumonia (one of them complicated by endocarditis and meningitis) and one of bronchopneumonia in man and one case of experimental bronchopneumonia (pneumococcic) in the rabbit. The control material consisted of two human brains (fixed two hours post mortem) from subjects of legal electrocution, six rabbit brains (fixed at various periods post mortem) and twenty-two mouse brains. The latter came from mice that had died of pneumococcic peritonitis or from normal mice, and were fixed either immediately or several hours post mortem. All tissue was fixed with Carnot's solution, and stains were made in duplicate with toluidine blue and with toluidine blue and phloxin. The animals were killed by a large intracardiac injection of a saturated solution of magnesium sulphate. The pons and the medulla oblongata in each case were fixed in successive disks averaging 3 or 4 mm. in thickness. The time of fixation in the

5. Ranson, S. W.: The Anatomy of the Nervous System, ed. 2, Philadelphia, W. B. Saunders Company, 1925, p. 330.

6. Tilney, F., and Riley, H. A.: The Form and Functions of the Central Nervous System, New York, Paul B. Hoeber, Inc., 1921, p. 324.

7. Lumsden, Thomas: J. Physiol. **57**:153 and 354, 1923; **58**:81 and 111, 1923.

human cases ranged from one to three hours post mortem. All sections were made from as near the surface of the blocks as it was possible to get complete sections.

THE BRAIN STEM OF THE MOUSE

The first studies were made on the brain stems of mice. Because of the technical difficulties, the small size of the nerve centers and the difficulty in handling, observations on the twenty-two mice yielded only two results of value: (1) instruction in the technic of preparation to insure uniformity of fixation and stain, and (2) the knowledge that up to two or three hours after death postmortem changes in the nerve cells, while in the later hours recognizable, are very slight and very different from the damage to be described in the pneumonic patients.

THE BRAIN STEM OF THE RABBIT

The medullary and pontile centers of six rabbits were studied. The observations were as follows:

Changes in the Cells.—1. Normal Rabbit (1); Immediate Fixation: The cells of the various nuclei were in extremely good preservation (fig. 1 *A*).

2. Normal Rabbits (2 and 3); Fixation Two and Four Hours Post Mortem: At two hours, there was little change; this consisted of slight perineural retraction in places and slight fuzzing and finer granularity of Nissl bodies, but within normal limits, so that, without labeling, sections could not be distinguished from those from an animal on which autopsy had been performed immediately (fig. 1 *B*). At four hours, the changes were similar to those at two hours, but more marked, so that cells could be definitely recognized as abnormal. Most cells, however, even at four hours showed remarkably little change, in spite of obvious changes in the white matter (fig. 1 *C*).

3. Rabbits (4, 5 and 6) Exposed to Carbon Dioxide (25 per cent) and Oxygen (75 per cent) for Two Hours; Immediate Autopsy: Very slight but recognizable changes were present in the Nissl substance, especially in the cells of the gray reticular substance, consisting of slight hyperchromatism or of chromatolysis in the early stages, similar to that seen post mortem in the normal rabbits. At two and four hours post mortem, these changes were slightly more marked but of the same character as the postmortem changes in the normal rabbits. (Carbon dioxide was given with 75 per cent oxygen, an amount far in excess of that necessary to prevent anoxemia. Occasional areas of chronic encephalitis were encountered in several of the rabbits, but the regions of these areas were strictly avoided in making observations.)

Other Changes.—These consisted of moderate vascular engorgement in the animals given carbon dioxide and varying amounts of vacuolization (false porencephalia) and axon swelling in the white matter due to postmortem disintegration.

Important Indications from These Data.—1. Postmortem changes in the cells of the brain stem of the rabbit up to two or three hours are so slight as to be almost negligible with the present method of prepara-

tion, and what changes there are, are recognizable. 2. In the rabbits exposed to carbon dioxide in an effort to exhaust respiratory neurons, there is a hint of particular damage to the *large and small cells of the reticular gray matter.* (See discussion of human material with particular reference to that of the respiratory center.)

THE BRAIN STEM OF MAN

Material from the human brain stem was studied in the following cases:

1. Woman, aged 65; lobar pneumonia; fixation one and one-half hours post mortem
2. Man, aged 35; lobar pneumonia; fixation one and one-half hours post mortem

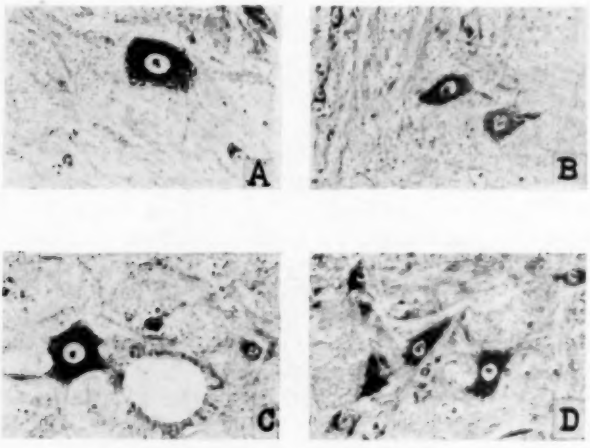

Fig 1.—Cells from the reticular gray matter of the medulla of the rabbit brain: *A,* photomicrograph of a normal large cell (normal rabbit), fixed immediately after the rabbit was killed; *B,* appearance of smaller cells, normal except for slight changes in the Nissl substance—from a normal rabbit, the tissues of which were fixed two hours post mortem; *C,* a large cell with slight change in the Nissl substance and slight perineural retraction, but with the structure remarkably well preserved—from a normal rabbit, the tissues of which were fixed four hours post mortem; the white matter shows large vacuoles; *D,* smaller cells showing loss of definition of the Nissl granules and slight nuclear changes—from a rabbit dead of bronchopneumonia, the tissues of which were fixed immediately.

3. Woman, aged 36; lobar pneumonia; fixation three hours post mortem
4. Woman, aged 31; bronchopneumonia; fixation three hours post mortem
5. Man, aged 57; lobar pneumonia; fixation two hours post mortem
6. Man, aged 57; lobar pneumonia, pneumococcic endocarditis (tricuspid) and pneumococcic meningitis; fixation one hour post mortem
7. Rabbit, adult; bronchopneumonia; immediate autopsy and fixation

The control tissue was from electrocuted persons and was fixed two hours post mortem.

The changes to be described are only those uniformly present throughout all six cases and are not of the type due to postmortem disintegration, seen in rabbits. The pneumonic rabbit showed slight changes consistent with those found in the human cases (fig. 1 *D*).

Changes in Cells (Exclusive of Pigmentation).—1. Sensory Nuclei (Nucleus Cuneatus, Nucleus Gracilis, Sensory Root of Fifth Nerve, Vestibular and Cochlear Nuclei): The control showed moderate shrinkage of cells and perineural retraction (edema?) with some decrease in Nissl substance and occasional cells with chromatolysis. The changes have the appearance of the postmortem changes seen in rabbits. The pneumonic person showed marked shrinkage of cells, perineural retraction, and chromatolysis that left shapeless, hyperchromatic masses as remnants of many of the cells. These changes were much more pronounced than in the control.

2. Somatic Motor Nuclei (Anterior Horn and Spinal Accessory Cells, Nucleus Ambiguus, Hypoglossal Nucleus, Nucleus of Facial Nerve, Nucleus Abducens):

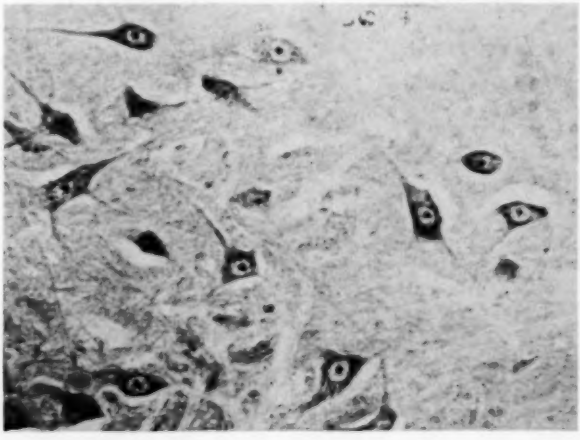

Fig. 2.—Somatic motor cells (hypoglossal nucleus) of the human brain stem from a person who died of lobar pneumonia. The cells are relatively intact, except for perineural retraction and occasional cell disintegration.

The control showed excellent preservation of cells except for slight shrinkage and perineural retraction. The Nissl substance was almost perfectly preserved. The pneumonic person showed the cells in good preservation, almost as good as in the controls, but with more perineural retraction (fig. 2).

3. Visceral Motor Nuclei (Vagus Motor Nucleus, Nucleus of Tractus Solitarius): The control revealed moderate loss of Nissl substance and an occasional shrunken cell. The cells were generally well preserved. The changes were probably due to postmortem disintegration. The pneumonic person's cells were similar to those of the control with slightly more change of the same character. The lesion was interpreted as an early postmortem change plus some general toxic damage.

4. Cells of Reticular Gray Matter (To Be Discussed): The control presented slight shrinkage of these cells and perineural retraction. The Nissl substance was fairly well preserved (figs. 3 and 4 *A*). The pneumonic person showed marked

swelling of large and small cells with rounding of the cell outlines, chromatolysis and migration of the nuclei to the cell margins, with shrinkage and condensation of the nuclei. The changes were most marked in the upper medullary (middle) expansion, but were present in corresponding levels of expansion in the midmedulla (lower expansion) and upper part of the pons (upper expansion) (figs. 3 and 4 *B*).

5. Cells of Central Gray Matter of Upper Part of Pons (Floor of Fourth Ventricle and Floor of Aqueduct of Sylvius Central to Locus Caerulus, and Nucleus of Median Raphe of Upper Part of Pons) (To Be Discussed with Section 4): The controls showed little change except for pigment (see later paragraphs on this), which was present to some extent. The pneumonic person showed swelling and irregularity of cell outlines, with migration of the nuclei to the cell margins and chromatolysis.

6. Olivary Bodies and Others: The controls showed changes similar to those in the sensory cells, but more marked. The pneumonic person also showed changes similar to those in the sensory cells, but more marked.

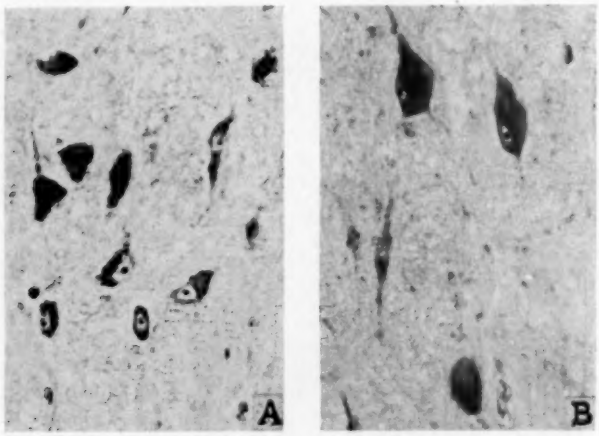

Fig. 3.—Cells of the reticular gray matter at the level of the upper part of the medulla oblongata in the human brain stem: *A*, relatively well preserved cells from a control; *B*, a corresponding area from the brain stem of a person who died of lobar pneumonia, showing swelling of cells, chromatolysis, nuclear displacement but with shrinkage of the nuclei and little perineural retraction.

Important Indications from These Data.—1. An extremely slight, though general, lessening of the sharp definition of the Nissl granules was present throughout all sections and was interpreted as representing the general toxic damage seen in all other tissues of the body (so-called cloudy swelling).

2. Varying amounts of perineural retraction (edema?) were seen, most marked in the sensory centers and least marked in the somatic motor cells. The assumption that the enlarged perineural spaces were the result of edema was borne out, as in Chornyak and Sayer's [3] work, by the presence of perivascular edema as well. The same appearance

was noted by Kubie [8] in his hydration experiments on animals. It must be remembered, however, that if the tissue is not perfectly fixed, cell shrinkage may occur which may simulate edema closely. The same observation was occasionally made in animals examined long post mortem, but not with any regularity in those examined within the periods of time of the human cases. The cells of the vagus motor nucleus, the nucleus ambiguus and the nucleus of the tractus solitarius showed slightly more damage than did the motor cells, but less than the sensory cells.

3. A *rather vaguely defined nucleus* in the reticular gray matter, made up of a column of cells running from the peduncles downward and outward to a position in midmedulla between the nucleus ambiguus and

Fig. 4.—Cells from fields *A* and *B* of figure 3, seen by oil immersion. Note the relative integrity of the Nissl granules, nucleus and cell outline in the control (*A*) as compared with the marked destruction in the pathologic tissue (*B*). Observe the collection of golden-brown pigment at one pole of the damaged cell.

the dorsal accessory olive and beyond, was noted particularly. This column appeared to have enlargements (*a*) at the upper level of the pons, (*b*) at a level immediately caudal to the striae acousticae and (*c*) at the lower limit of the inferior olive, at the pyramidal decussation just internal to the spinal accessory motor cells. The cells of this column showed extreme degenerative changes, comprising marked swelling, partial or complete chromatolysis and eccentric, distorted nuclei. There was little perineural retraction here. The changes in this group of cells will be discussed in detail in later paragraphs. Extension of this group

8. Kubie, L. S.: Brain **51**:244, 1928.

of cells into the floor of the aqueduct of Sylvius, medial to the cells of the locus caeruleus, and the nucleus of the median raphe also showed a marked degree of the same type of damage.

Pigmentary Changes.—1. Normal Pigment: This was seen in cells of the locus caeruleus (substantia ferruginea) and in occasional scattered cells throughout. It appeared as coarse brownish-black granules loading the cytoplasm of the cells. It was seen in both animal and human material, and in both control and pathologic tissue.

2. Abnormal Pigment: Delicate golden-brown pigment occurred in masses of extremely fine granularity in the cytoplasm of many of the neurons, displacing and often replacing the Nissl substance. It was abundant in badly damaged cells and in cells of older persons and was most marked in those of a partially demented person who died of pneumonia.

This golden pigment was much more abundant in cells of persons who died of pneumonia than it was in the cells of controls of the same range of age. However, the amount of chromatolysis and nuclear damage was not always proportionate to the amount of pigment. The pale-golden pigment has been said by various European authors (for instance, Kaufmann [9]) to be present more commonly in persons of advanced age, in demented persons and in those dying of acute infectious diseases, particularly typhoid fever. It is supposed to represent an accumulation of uneliminated waste products. Its exact character is not known, although probably it belongs to the lipochromes. It was never seen in animal tissue.

Other Changes.—1. Moderate engorgement of blood vessels was noted, with edema of perivascular spaces.

2. Occasional vacuolization of white matter was seen in both control and pathologic tissues, but it seemed to have no relation to cell preservation.

3. One pneumonic person and one control showed slight perivascular round cell infiltration in the meninges (probably syphilis or, in the pneumonic person, a feature of the "toxic encephalosis" described by Winkelman,[10] without apparent influence on the nerve cell changes.

4. One pneumonic person showed a massive polymorphonuclear meningeal exudate, *but the cells of the parenchyma showed only the same changes as did those of pneumonic persons without meningitis.*

5. Practically no increase in satellite glia cells was found.

COMMENT

The first point essential in dealing with human tissue is the recognition of the normal conditions and of the character and time of appearance of postmortem changes, since human material can practically never

9. Kaufmann, Edward: Pathology for Students and Practitioners, translated by Stanley P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 3, p. 1871.

10. Winkelman, N. W.: Pennsylvania M. J. **33**:208, 1930.

be fixed as rapidly after death as that from the experimental animal. The work on the mice and rabbits made me realize two points: (1) that in brain tissue up to two to three hours after death changes due to postmortem disintegration were slight and were recognizable, and (2) that the profound changes seen in the cells of the human material were emphatically not due to postmortem disintegration. It must be remembered that human subjects of electrocution are supposed to die as the result of central respiratory failure, so that the control tissue might be expected to show some changes in the nuclei associated with respiratory control. The rapidity of death probably accounts for the fact that these cells were so little damaged.

Secondly, it was very striking that these changes, with certain exceptions to be noted, were identical, though less intense, with the results of Chornyak and Sayer [3] in animals asphyxiated by carbon monoxide. The changes were not so profound as those that they observed, but the anoxemia of pneumonia is much less intense than that to which their animals were subjected. It is further interesting that in the rabbits subjected to carbon dioxide, with plenty of oxygen to prevent cellular asphyxia, these changes did not occur except for slight damage to the group of cells of the reticular gray matter. The one outstanding observation in the human material differing from Chornyak and Sayer's report was that only slight change was seen in the cells of the vagus motor nucleus and the nucleus of the tractus solitarius as opposed to the profound disturbances observed by them. This may perhaps be explained by the less intense degree of a similar damaging agent (namely, anoxemia) acting on cells perhaps a little more resistant in man than in the dog. It is possible, too, that certain cells are essentially more susceptible to damage of *any* sort than others, and that much the same changes are found regardless of whether the damaging agent is anoxemia or bacterial toxemia. Certainly it appears that in pneumonia the most profound nerve cell damage occurs in almost the same areas as those so severely damaged by simple anoxemia.

Particular attention must now be called to that irregular column of cells in the gray reticular substance. Chornyak referred to the central expansion of this "nucleus" as an unidentified nucleus lying in the gray reticular substance between the dorsolateral accessory plate of the inferior olive and the nucleus ambiguus, and described profound damage to these cells as compared with closely adjacent ones. In the human series I observed very severe damage to these cells and to corresponding ones in the upper and lower expansions of this mass as well. When one remembers that the consensus places the respiratory center just in this area, it becomes increasingly interesting. Moreover, Lumsden [7] demonstrated in the mammal that physiologically the respiratory mechanism can be divided into four philogenetic levels: (*a*) a regulatory

center in the upper part of the pons (upper expansion?), (*b*) an inspiratory and expiratory center close together at the level of the striae acousticae and just below it (middle expansion?) and (*c*) a gasping center near or caudal to the posterior limit of the fourth ventricle (posterior expansion?). A combined view of these bits of evidence gives one a strong suggestion that this tripartite "nucleus" may be the actual center of the respiratory and perhaps of the vasomotor mechanism, and that it bears *extremely severe damage* both in pure anoxemia and in pneumonia.

In comment I do not wish to intimate that the brain is the only organ damaged by the noxious agents in either pneumonia or anoxemia. I believe that the liver, peripheral blood vessels and kidneys are greatly damaged, together with all the tissues of the body, and that malfunction of these probably adds the toxic products of faulty function and metabolism to those of bacterial origin.

CONCLUSIONS

In death from pneumonia (six cases) there was marked damage to the cells of the medullary and pontile centers, the cells of the various nuclei showing varying degrees of change. The most severe and the least severe damage occurred in corresponding nuclei in the six cases. Cells in the sensory nuclei showed more damage than those in the motor nuclei. Cells of the reticular gray matter, which has been described by others as the probable site of the respiratory and vasomotor centers, showed the most severe degenerative changes.

VIOSTEROL IN EXPERIMENTAL FIBROUS OSTEITIS

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Recent study of osteitis fibrosa cystica has shown this condition to be a manifestation of hyperfunction of the parathyroid glands (Barr and Bulger;[1] Hunter and Turnbull[2]). Experimental proof of this relationship was first offered by Jaffe, Bodansky and Blair,[3] who produced the lesions of fibrous osteitis in young guinea-pigs and dogs by injections of parathormone. We began the investigations reported in this paper with the objects of reproducing the work of Jaffe and his co-workers and of discovering whether the administration of viosterol would prevent the bone lesions induced by parathormone.

METHODS

Young guinea-pigs weighing between 200 and 350 Gm. were used. The diet consisted of oats, hay, carrots, cabbage and water, ad libitum. The animals were weighed once a week. Parathormone was injected subcutaneously. Viosterol 250 D was diluted in maize oil so that the desired dosage was contained in 0.2 cc. It was given orally by means of a Luer syringe. The animals received viosterol for ten days before the injections of parathormone were begun. At the end of the experiment, they were bled to death and examined immediately. The bones were fixed in Zenker's solution plus 5 per cent glacial acetic acid, and decalcified in Müller's fluid. Paraffin sections of the ribs and long bones were stained with hematoxylin and eosin.

The soft tissues were fixed in alcohol, and paraffin sections were stained by the von Kossa method as well as in hematoxylin and eosin. However, no calcium deposits or other changes relevant to this work were observed.

The parathormone used in this work was donated by Eli Lilly & Company. Mead Johnson & Company supplied the viosterol.

PRODUCTION OF THE LESIONS OF FIBROUS OSTEITIS

Animals 1, 2, 3, 4 and 5 were used in this experiment. The schedule of the daily doses of parathormone is given in the table. Animals 2 and 3 each received only 326 units of parathormone over a period of twenty-five days. The bone changes were comparatively slight. In the ribs, there was some thinning of the cortex with

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From Beth Israel Hospital.

1. Barr, D. P., and Bulger, H. A.: Am. J. M. Sc. **179**:449, 1930.
2. Hunter, D., and Turnbull, H.: Brit. J. Surg. **19**:203, 1931.
3. Jaffe, H. L.; Bodansky, A., and Blair, J. E. Arch. Path. **11**:207, 1931; J. Biol. Chem. **88**:629, 1930; J. Exper. Med. **52**:669, 1930.

Dosage Schedules

Guinea-Pig	Units of Parathormone Administered on Given Day of Injection																															Daily Dose of Viosterol, Mg.	Total Units of Parathormone
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31		
1	4	6	6	8	9	10	10	10	10	15	15	20	20	20	25	25	28	30	40	50	50	50	60	40	40	K	..	..	..	..	..	0	581
2	4	4	4	4	4	4	4	8	10	10	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	0	K	..	0	326
3	4	4	4	4	4	4	4	8	10	10	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	0	K	..	0	326
4	4	6	6	10	10	10	10	10	15	20	25	30	30	40	0	40	0	0	0	20	40	40	40	20	20	20	K	..	..	..	..	0	466
5	4	8	10	10	10	10	10	10	15	20	25	30	35	40	40	40	40	40	60	60	60	80	72	80	K	..	..	..	..	..	..	0	849
6	4	6	6	8	10	10	10	10	15	20	25	30	30	40	0	40	0	0	0	20	40	40	40	20	20	20	K	..	..	..	..	20	466
7	4	6	6	4	4	4	4	8	10	10	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	0	K	20	345
8	4	6	6	8	10	10	10	10	15	20	25	30	30	40	0	40	0	0	0	0	40	40	40	20	20	20	K	..	..	..	..	2	466
9	4	6	6	4	4	4	4	8	10	10	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	0	K	2	345
10	4	6	6	10	10	10	10	15	20	25	30	30	40	0	40	0	0	0	20	40	40	40	20	20	0	20	K	..	..	..	..	8	466
11	4	4	4	4	4	4	4	8	10	10	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	0	15	15	15	0	K	8	326
12	4	8	10	10	10	10	10	10	15	20	25	30	35	40	40	40	40	40	60	60	60	80	72	80	K	..	..	..	..	..	..	15	849
13	4	6	6	8	9	10	10	10	10	15	15	20	20	20	25	25	28	30	40	50	50	50	60	40	40	K	..	..	..	..	..	15	581
14	4	6	6	8	9	10	10	10	10	15	15	20	20	20	25	25	28	30	40	50	50	50	60	40	40	K	..	..	..	..	..	15	581
15	4	6	6	10	10	10	10	10	15	20	25	30	30	40	0	40	0	0	0	20	40	40	40	20	20	K	..	..	..	..	..	15	581
16	..	6	6	8	9	10	10	10	10	15	15	20	20	20	25	25	28	30	40	50	50	50	60	40	40	0	K	..	..	..	..	0	581
17	4	6	6	10	10	10	10	10	15	20	25	30	30	40	0	40	0	0	0	20	40	40	40	20	20	20	K	..	..	..	..	0	464
18	4	6	6	10	10	10	10	10	15	20	25	30	30	40	0	40	0	0	0	20	40	40	40	20	20	20	K	..	..	..	..	15	464
19	10	0	10	20	0	0	40	0	0	60	0	0	80	0	0	80	0	0	0	80	0	0	K	..	..	..	..	..	..	..	..	0	380
20	10	0	10	20	0	0	40	0	0	60	0	0	80	0	0	80	0	0	0	80	0	0	K	..	..	..	..	..	..	..	..	15	380
21	10	10	10	20	30	40	0	50	0	60	0	80	0	40	20	10	10	10	10	10	10	10	10	10	10	10	K	..	..	..	..	0	480
22	10	10	10	20	30	40	0	50	0	60	0	80	0	40	20	10	10	10	10	10	10	10	10	10	10	10	K	..	..	..	..	15	480
23	10	10	10	20	30	40	0	50	0	60	0	80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	K	..	..	..	..	0	310
24	10	10	10	20	30	40	0	50	0	60	0	80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	K	..	..	..	..	15	310
25	10	10	10	20	30	40	0	50	0	60	0	80	0	K	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	0	310
26	10	10	10	20	30	40	0	50	0	60	0	80	0	K	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	15	310

evidences of subperiosteal resorption. The slightly widened haversian canals contained fibrous tissue. At the costochondral junction there was thinning of the trabeculae, which were surrounded by a few strands of fibrous tissue. The marrow showed some congestion. In the long bones, there was a relatively small amount of fibrous replacement of the marrow at the metaphysis close to the epiphyseal cartilage.

Animals 1 and 5 received 581 units and 849 units of parathormone, respectively, over a period of twenty-five days. The bones showed extremely severe lesions of fibrous osteitis. In the ribs, there was marked thinning of the cortex with fragmentation and deforming spontaneous fracture. The numerous osteoclasts in their deeply excavated Howship's lacunae further confirmed the active resorption of bone. Columns of closely packed fibrous tissue filled the widened haversian canals. At the costochondral junction, the trabeculae were fragmented and disorganized. Starting from this region and extending, especially in animal 5, far into the shaft, the marrow was almost completely obliterated by a large amount of dense connective tissue. The changes in the long bones were not as striking as those in the ribs. Although there were signs of subperiosteal resorption of bone, and although the widened haversian canals were filled with connective tissue, there was no obvious thinning of the cortex. The bone trabeculae, however, displayed definite decalcification. The marrow adjacent to the epiphyseal plate was usually replaced by fibrous tissue, which, however, did not extend into the shaft. No fibrosis of the marrow of the shaft proper was found.

Animal 4 received 466 units of parathormone over a period of twenty-six days. Lesions, equal in severity to those in animals 1 and 5, were found. In addition, at the costochondral junctions of the ribs, several definite cysts were observed embedded in dense fibrous tissue (fig. 1).

X-ray pictures of the animals in this group, taken after death, showed no changes in the bones.

The bone lesions produced by parathormone in the animals of this group agree in all essentials with those reported by Jaffe and his co-workers. However, although animals 4, 1 and 5 received different amounts of parathormone—466, 581 and 849 units, respectively—the lesions in all of them were of the same order of magnitude. It seems, therefore, that above a certain limit of dosage, the extent of the changes in the bones does not necessarily run parallel to the amount of parathormone injected.

EFFECT OF VIOSTEROL IN EXPERIMENTAL FIBROUS OSTEITIS

It is well known that adequate though relatively small doses of viosterol cause increased calcification of bone, at least in rickets and osteomalacia. Large doses of parathormone produce decalcification of bone. The possible antagonism between these two substances raised the question whether the administration of viosterol could prevent the decalcification and fibrous osteitis caused by parathormone.

The literature offers conflicting reports on this subject. Hoff and Homann [4] reported increased calcification, as judged by x-ray pictures,

4. Hoff, F., and Homann, E.: Ztschr. f. d. ges. exper. Med. **74**:258, 1930.

in the bones of adult rats from viosterol. Simultaneous injection of parathormone in another group of rats that received the same dose of viosterol prevented increased calcification of bone. No microscopic examinations or chemical analyses of the bones were made, and the x-ray picture, we hold, is not a delicate criterion of bone decalcification in

Fig. 1.—The costochondral junction of a rib of animal 4 under high power magnification. Note the cysts embedded in the fibrous tissue that has replaced the marrow.

small animals. The amount of viosterol, evidently 40,000 curative rachitic doses, given daily by these workers is highly toxic, and several of the animals died within a few days. That such massive doses of vitamin D should bring about calcification of bone is contrary to the findings of other workers, who almost uniformly report decalcification as

a result of such doses. Even though this objection is disregarded, the method used by Hoff and Homann is not a satisfactory one for demonstrating antagonism between parathormone and viosterol. It seemed better to attempt to counteract the decalcifying action of parathormone by means of viosterol than to prevent, by the use of parathormone, any possible increased calcification that might occur from vitamin D. Marked increase in calcification in normal animals from viosterol is certainly not a prominent finding. On the other hand, the decalcifying action of parathormone is definite and, within limits, may be brought to any desired degree.

The possible antagonism between these two substances has also been considered by clinicians. Regnier [5] observed a patient with von Recklinghausen's disease who was apparently benefited by vigantol. X-ray films demonstrated the improvement. Hunter and Turnbull [2] mentioned a possibly favorable effect in one patient following the use of ultraviolet irradiation and preparations of vitamin D. They suggested the use of viosterol when parathyroidectomy is contraindicated. Cystic degeneration of bone in the patient of Snapper and Boeve [6] progressed for seven weeks after parathyroidectomy, but was checked in two months by vigantol. Wilder [7] noticed improvement following the use of vitamin D in his case of generalized osteitis fibrosa cystica. Quick and Hunsberger [8] suggested a probable antagonism between vitamin D and the parathyroid hormone.

Other observations fail to indicate any therapeutic effect of vitamin D in osteitis fibrosa cystica. Snapper [9] found that viosterol did not influence the course of the disease. Prolonged use of large doses of cod liver oil, viosterol and ultraviolet irradiation failed in one of Hunter and Turnbull's [2] patients.

We attempted to discover whether the fibrous osteitis produced in guinea-pigs by parathormone could be prevented by viosterol.

Apparently rickets has never been produced in the guinea-pig, and viosterol has seldom been given to this animal. Kreitmair and Moll [10] used guinea-pigs in their studies of the toxic effects of massive doses of viosterol. We desired to avoid toxic dosages, as these bring about bone decalcification. Our dosages were arrived at as follows: Calculated on the basis of an average daily food consumption of 7 Gm., the minimum daily dose of viosterol, 250 D, that will cure rickets in rats is 0.17 mg. of the oily solution (McCollum's diet 3143 and five day test

5. Regnier, E.: Fortschr. a. d. Geb. d. Röntgenstrahlen **39**:696, 1929.
6. Snapper, I., and Boeve, H. J.: Deutsches Arch. f. klin. Med. **170**:371, 1931.
7. Wilder, R. M.: Endocrinology **13**:231, 1929.
8. Quick, A. J., and Hunsberger, A.: J. A. M. A. **96**:745, 1931.
9. Snapper, I.: Arch. Int. Med. **46**:506, 1929.
10. Kreitmair, H., and Moll, T.: München. med. Wchnschr. **75**:637, 1928.

period).[11] Since our guinea-pigs weighed approximately ten times more than the young rats used in the standardization of viosterol, we arrived at 1.7 mg. as a theoretically minimal basic dose. As it was desired to give sufficient vitamin D to produce an effect, doses varying from 2 to 20 mg. of viosterol were employed. These, it was felt from the work of Bills and Wirick[12] on rats, would entail no danger of toxic effects.

In this experiment, 9 animals were used (6, 7, 8, 9, 10, 11, 12, 13 and 14). All but animals 11, 10 and 6 received parathormone (table). These three animals were given viosterol alone in doses of 2, 8 and 20 mg., respectively. Microscopic examinations of the ribs and long bones revealed no abnormalities. Doses of parathormone similar to those given animals 2 and 3, i. e., from 326 to 345 units over a period of twenty-nine days, were given to animals 12, 14 and 8, which, in addition, received daily doses of 2, 8 and 20 mg. of viosterol, respectively. The mild lesions of bones observed in animals 2 and 3 were present here. Although the changes in the bones of 12, 14 and 8 may possibly have been less than in the two controls, the differences were too slight to be considered significant. Animals 7, 9 and 13, which received daily 2, 8 and 20 mg. of viosterol, respectively, were given the same schedule of parathormone dosage as guinea-pig 4, i. e., 466 units over a period of twenty-six days. In these three animals, lesions were almost completely absent in the ribs, and the changes in the long bones were much less than in the control. This apparent antagonism could not be demonstrated in later experiments, and we can offer no satisfactory explanation for its occurrence.

In order to obtain more definite and extensive information on the question of an antagonistic action between viosterol and parathormone another group of five animals was taken (15, 16, 17, 18 and 19). No. 19, serving as a control of the potency of the parathormone, received 581 units in twenty-five days, the same amount as guinea-pig 1 in a previous group. Typical and severe lesions of fibrous osteitis were produced. Animals 16 and 17 were similarly treated, but in addition received 15 mg. of viosterol daily. Striking lesions of fibrous osteitis were found and were of unusual severity, especially in the long bones. In fact, the changes in the long bones were the most pronounced we had yet encountered. The cortex was shattered and fragmented and, in certain areas, occupied by compact masses of fibrous tissue. Numerous osteoclasts bore evidence of active resorption of bone. The trabeculae had disappeared almost completely, and the fibrous replacement of the marrow had gone so far as to convey the impression that the entire metaphysis was one solid mass of connective tissue. Animals 18 and 15 received 15 mg. of viosterol daily in addition to 466 and 849 units of parathormone, respectively, over a period of twenty-five days. Severe lesions of fibrous osteitis were found, more extensive in the long bones than in the ribs. The changes in the long bones were, in fact, more pronounced in 18 and 15 than in controls 4 and 5, which received no viosterol.

In a group of ten animals, various modifications of the schedules of parathormone dosage were used in a further attempt to demonstrate a possible antagonism between this substance and viosterol. The animals were run in pairs, one receiving parathormone alone, and the other the same amount of parathormone plus 15 mg. of viosterol. Animals 20 and 21 were given 464 units of parathormone over a period of twenty-six days, the latter animal, in addition, receiving 15 mg. of viosterol daily. Severe lesions of fibrous osteitis were found in the ribs and long bones of both animals.

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11. Bills, C. E.: Personal communication.
12. Bills, C. E., and Wirick, A.: J. Biol. Chem. **86**:117, 1930.

It will be observed from the table that animals 22 and 23 received 380 units of parathormone in large doses at intervals over a period of twenty-two days. The animals were allowed to rest for from two to three days between the injections of 60 or 80 units of parathormone. No. 23 received, in addition, 15 mg. of viosterol daily. In animal 22, the lesions of fibrous osteitis were marked. In the ribs, the cortex was thinned, and the greatly widened haversian canals were filled with cel-

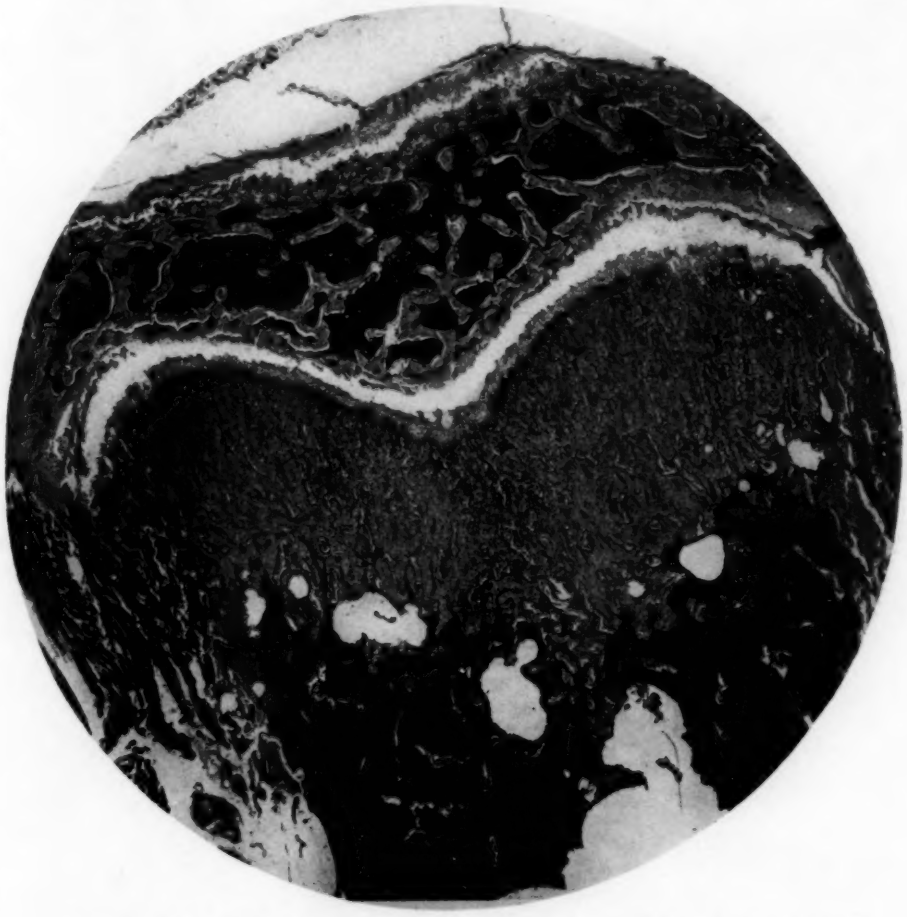

Fig. 2.—The proximal end of a tibia of animal 16. The bony trabeculae and marrow of the metaphysis are almost completely replaced by fibrous tissue.

lular connective tissue. Numerous osteoclasts were seen in the haversian canals as well as in the subperiosteal and endosteal regions. Similar evidences of resorption were visible around the trabeculae at the costochondral junction, and the marrow in this area was replaced by fibrous tissue. In the long bones, the greatly widened haversian canals were likewise packed with connective tissue. So marked was this process that in places the cortex was almost completely replaced by fibrous tissue. Numerous osteoclasts in Howship's lacunae surrounded the trabeculae and were present in the endosteal and subperiosteal regions. The usual replacement of the

metaphyseal marrow by fibrous tissue was observed. The marrow of the shaft was congested. A few islands of connective tissue could be discerned in the outer rim of the epiphysis. In animal 23, in spite of the daily administration of 15 mg. of viosterol, striking lesions of fibrous osteitis were present in the ribs and long bones. In fact, the resorption of bone and fibrous replacement of the marrow were

Fig. 3.—High power magnification of section shown in figure 2. Note epiphyseal cartilage in lower right corner, almost complete absence of bony trabeculae and fibrous tissue replacement of marrow.

essentially as severe in this animal as in control 22, which received parathormone alone.

Animals 24 and 25 received rapidly increasing doses of parathormone up to the twelfth day when 80 units were given. During the next three days the dosage was dropped to 10 units daily, at which level it was maintained until the end of the experiment on the twenty-sixth day (table). Animal 25 was given, in addition, 15 mg. of viosterol daily. The lesions of fibrous osteitis in this animal were much

more severe than those in animal 24, which received no viosterol. In fact, the changes in the bones of animal 24, which received parathormone alone, were slight, whereas the lesions in animal 25, especially those found in the long bones, were extensive. The occurrence of such slight lesions in the animal receiving parathormone alone might be explained on the basis of recent investigations published by Jaffe and his co-workers.[13] They suggested that in protracted experiments with

Fig. 4.—The cortex of a rib of animal 25. Periosteum and muscle fibers are seen on the left. The tremendously enlarged haversian canals are filled with vascular fibrous tissue.

parathormone on guinea-pigs a compensatory mechanism allows healing of lesions produced earlier in the treatment.

It is quite possible that this may have occurred in animal 24, which received only 10 units of parathormone daily during the last eleven days of the experiment.

13. Jaffe, H. L.; Bodansky, A., and Blair, J. E.: J. Exper. Med. **55**:139, 1932.

Any compensatory mechanism that takes place evidently did not function so well in animal 25, which was given 15 mg. of viosterol daily. A synergistic action between parathormone and viosterol should possibly be considered in this instance.[14]

Animals 26 and 27 received increasing doses of parathormone up to a maximum of 80 units on the twelfth day, and no further injections during the remaining fourteen days of the experiment (table). Animal 27 was given 15 mg. of viosterol

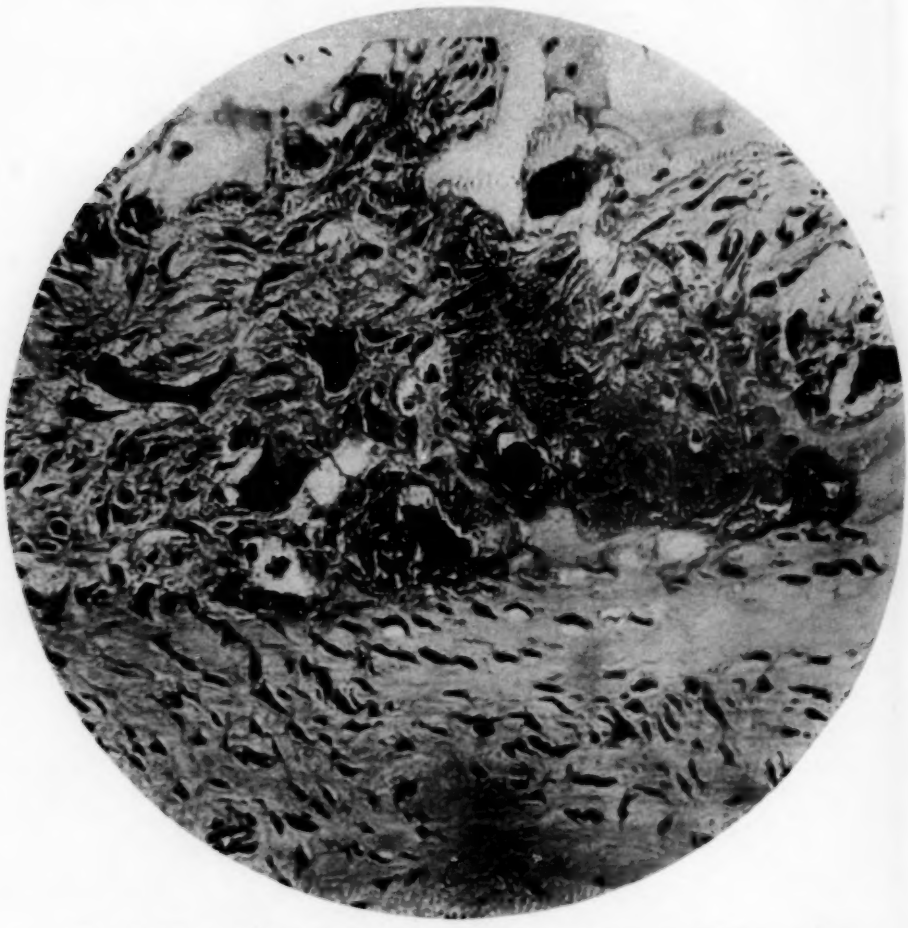

Fig. 5.—The metaphysis of a tibia of animal 27. An area of fibrous replacement containing many osteoclasts. Some of these are seen in Howship's lacunae.

daily, in addition. Both animals showed moderately severe lesions of fibrous osteitis, which were much more extensive in the long bones than in the ribs.

The table shows the dosage of parathormone given to animals 28 and 29. They received doses identical with those given the previous two pairs up to the fifteenth

14. Taylor, N. B.; Weld, C. B.; Branion, H. D., and Kay, H. D.: Canad. M. A. J. **25**:1, 1931.

day, when the experiment was terminated. Animal 29 received 15 mg. of viosterol daily. Lesions of the severest grade were present in the ribs and long bones of no. 28. Animal 29, which received viosterol, showed lesions of fibrous osteitis of moderate severity, but in this case they were unquestionably less marked than those in animal 28 receiving parathormone alone.

Fig. 6.—The cortex just below the costochondral junction of animal 28. Note the dense fibrous tissue surrounding the bony trabeculae.

SUMMARY

Three (7, 9 and 13) of five animals receiving viosterol plus 466 units of parathormone showed practically negligible changes in the bones compared with the control animals (4 and 20), which were given no viosterol. The lesions in the remaining two animals (18 and 21) were at least as severe as those found in the control. Two animals (28 and

29) were given rapidly increasing doses of parathormone over a period of fourteen days, the latter receiving viosterol. The lesions in this animal were strikingly less marked than those in its control. Throughout our work, it was only in this instance and in three of the animals of the previous group that viosterol seemed to show an antagonism to the action of parathormone.

Four animals (1, 19, 16 and 17) received 581 units of parathormone, the latter two being given viosterol. These two showed, if anything, even more severe fibrous osteitis than the two controls.

Two animals (5 and 15) received 849 units of parathormone. In the animal given viosterol (15) more extensive lesions were found than in the control.

Five animals (2, 3, 8, 12 and 14) received 326 units of parathormone. The lesions of the bones in all of them were comparatively mild, and were not significantly less in the three treated with viosterol (8, 12 and 14).

Animal 22 received rapidly increasing doses of parathormone, totalling 380 units. Equally severe lesions of the bones were found in this animal and in 23, to which viosterol was given.

In animal 24, which received 480 units of parathormone, the changes in the bones were comparatively slight. The lesions in animal 25, which received viosterol in addition, were severe.

Two animals (26 and 27) were given 310 units of parathormone over a period of twelve days, and then allowed to rest for fourteen days. Identical lesions of moderate severity were found in the bones of both animals in spite of the fact that viosterol was administered daily to animal 27.

COMMENT

Lesions of fibrous osteitis can be produced at will in guinea-pigs by repeated injections of parathormone. As the parathyroid hormone and vitamin D are antagonistic in several respects, an attempt was made to determine whether these lesions could be prevented by viosterol. The latter causes fixation of calcium in the bones, at least in rickets and osteomalacia, while the parathyroid hormone brings about mobilization of calcium from the bones. Viosterol produces a rise of serum phosphorus, whereas with parathormone a diminution is obtained. That both potent substances can raise the serum calcium, does not, as Hoff and Homann have remarked, mitigate against an antagonism. Parathormone increases the liberation of calcium from bone, whereas therapeutic doses of vitamin D increase the absorption of calcium from food.[15] In both instances, the blood may contain an increased amount of calcium. Since

15. Bauer, W., and Marble, A.: J. Clin. Investigation **11**:21, 1932.

the hypercalcemia following overdosage with viosterol is probably dependent on demineralization of the skeleton,[16] small amounts of viosterol were given.

In this work, the lesions of fibrous osteitis were not prevented by viosterol. Although a few of the animals given viosterol showed less severe lesions, the changes in the bones of the great majority were unaffected. Jaffe and his co-workers reached the same conclusions.[17] Johnson and Wilder [18] apparently obtained essentially similar results, according to their preliminary report.

CONCLUSIONS

Repeated injections of parathormone produced the bone lesions of generalized fibrous osteitis in guinea-pigs.

Viosterol did not prevent these lesions.

An antagonism between vitamin D and the parathyroid hormone was not demonstrated by the method used in this work.

16. Hess, A. F.; Benjamin, H. R., and Gross, J.: J. Biol. Chem. **94**:1, 1931.

17. Jaffe, H. L.; Bodansky, A., and Blair, J. E.: Proc. Soc. Exper. Biol. & Med. **29**:202, 1931.

18. Johnson, J. L., and Wilder, R. M.: Am. J. M. Sc. **182**:800, 1931.

EXPERIMENTAL PATHOLOGY OF THE LIVER

IX. RESTORATION OF THE LIVER AFTER PARTIAL HEPATECTOMY AND PARTIAL LIGATION OF THE PORTAL VEIN

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Although it has been demonstrated [1] that restoration of the liver after either mechanical or toxic injury is actually restoration of the tissue, and that such recovery progresses more rapidly on a diet high in carbohydrates, only indefinite evidence has been published concerning the effect of alteration of the amount of blood reaching the liver by way of the portal vein.[2]

Following the report by Higgins and Anderson [3] on their success with partial hepatectomy in standardized white rats, it seemed that some application of their quantitative methods of investigation might be applied to the problem of the effect of partial ligation of the portal vein on restoration of the liver following partial removal.

METHOD OF EXPERIMENT

In order to be sure of the ratio of the weight of the liver to the total weight of the animal, twenty-five rats from the stock pens were weighed and killed by exsanguination and their livers removed cleanly, rinsed lightly once, and weighed after light sponging to remove excess water. From the sum of the ratios of the weight of the liver to that of the body, a mean ratio of 0.0419 was derived. By applying the methods published by Dunn [4] in 1929, it was ascertained that this ratio was not only significant for all body weights within the limits of the group, but that there was a high correlation coefficient of 0.8726. From the same material it was possible to develop a formula by which to estimate the weight of the liver by the weight of the body of any given animal.

Work done in the Division of Experimental Surgery and Pathology.

1. Fishback, F. C.: Arch. Path. **7**:955, 1929. Mann, F. C.: Am. J. M. Sc. **161**:37, 1921. Ponfick, E.: Virchows Arch. f. path. Anat. **118**:209, 1889. Rous, P., and Larrimore, L. D.: J. Exper. Med. **31**:609, 1920.
2. Mann, F. C.; Fishback, F. C.; Gay, J. G., and Green, G. F.: Arch. Path. **12**:787, 1931.
3. Higgins, C. M., and Anderson, R. M.: Proc. Staff Meet., Mayo Clin. **5**:243, 1930.
4. Dunn, H. L.: Physiol. Rev. **9**:275, 1929.

The finding that the relation of the weight of the liver to the weight of the body is practically constant, at least among the young adults that were observed, is amply borne out by Donaldson.[5]

After the establishment of standards, a series of rats was operated on according to the technic of Higgins and Anderson, with the additional procedure of partially occluding the portal vein by ligature as in the first stage of the operation described by Dragstedt.[6] After partial hepatectomy and weighing of the hepatic tissue removed, the portal vein was accurately identified, a point above the last tributary selected, and a linen ligature passed about it. This ligature was tied over a wire, which was then removed (fig. 1). The wire was so selected as to approximate half of the diameter of the vein. The abdominal wall was then closed in two layers. Following operation, the rats received

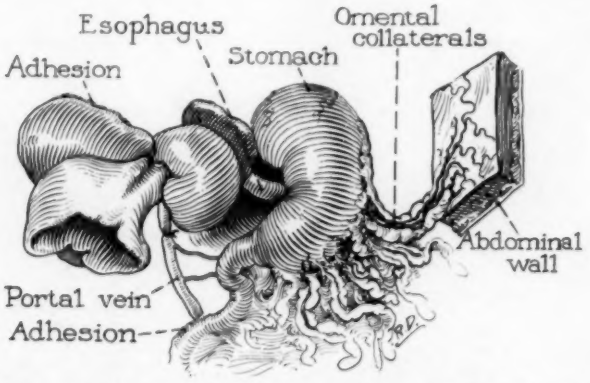

Fig. 1.—This semidiagrammatic view of the liver, stomach and omentum shows the operative procedure. Resection of the liver is completed, and the portal vein is partially ligated. The omental collateral vessels that develop following the operation and the small adhesions between the duodenum and the free edge of the liver are shown. These adhesions, separated for exposure, usually contain collateral vessels.

a solution of dextrose in water for the first twenty-four hours; they were then returned to the stock ration and tap water.

The mortality during the operation and in the succeeding twenty-four hours was rather high, as might be expected in such radical procedures on small animals. Necropsy was unsatisfactory except in the presence of peritonitis, which was unusual.

Groups of rats were killed at three, eight, fourteen, twenty-one and twenty-eight days after operation. These periods were selected as

5. Donaldson, H. H.: The Rat: Data and Reference Tables for the Albino Rat, Memoirs of the Wistar Institute of Anatomy and Biology, ed. 2, Philadelphia, 1924.

6. Dragstedt, L. H.: Science **73**:315, 1931.

most likely to reveal significant changes and as making it possible to compare the results with those of Higgins and Anderson. Each rat was lightly anesthetized and weighed, the abdomen opened, and the amount of collateral circulation determined. The animal was then killed by exsanguination, and the liver was dissected free from all attachments, rinsed once, dried lightly and weighed. Specimens were taken from typical livers in each group, and paraffin sections were stained with hematoxylin and eosin. These sections were compared with sections taken from the livers of normal rats used for the standard series.

After the expected weight of the liver had been calculated from the weight of the animal according to the formula derived from the standard series, it was possible to estimate the variation from the expected weight in each rat, and to determine the amount of change from the estimated weight of the remnant left at operation.

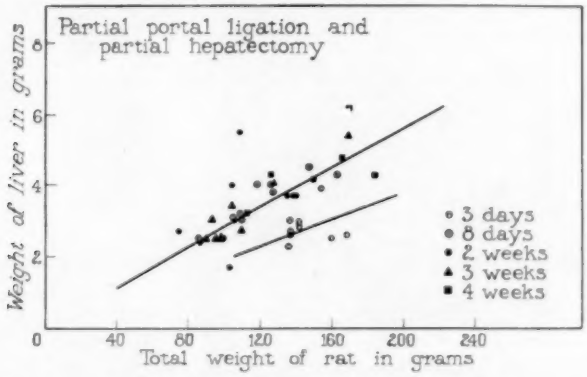

Fig. 2.—The graph shows the ratios after operation. In all cases, the weight of the liver was plotted against the weight of the body. The ratios cluster about one line, irrespective of the time interval, except for the first three days; in the three day group, the mean ratio is shown as a short line below the other. In each group, cases are well distributed as to weight of body.

OBSERVATIONS

Before operation, the ratio of the weight of the liver to that of the body was, as has been stated, 0.0419; the mean ratio of the remnants after operation was 0.0113 for the whole series. In eight rats killed on the third day after operation, the ratio was found to have increased to 0.0190. By the eighth day, in a group of ten rats, the ratio had further increased to 0.0289, but it changed little thereafter (figs. 2 and 3). After the eighth day, the curve of growth of the liver became almost a straight line at about 72 per cent of the expected ratio.

Considering the actual average weights of the liver in the various groups, there was a sharp rise in the mass of the remnants until the

eighth day, amounting to 2.38 Gm., after which there was a gradual fall again to 1.74 Gm. at four weeks. This represents an increase of about 300 per cent at the high point, but it is only about two thirds of that reported by Higgins and Anderson.

The effect of the operative procedure on the weight of the whole animal was definite and lasting. There was a decrease in total weight, starting immediately after operation, reaching its maximum at the second week, and returning toward normal after that time. However, at the end of the experiment, the average weight remained 5.98 Gm. below the preoperative level.

The response in restoration of the liver was correlated roughly with the amount of collateral circulation that had developed; it was evident

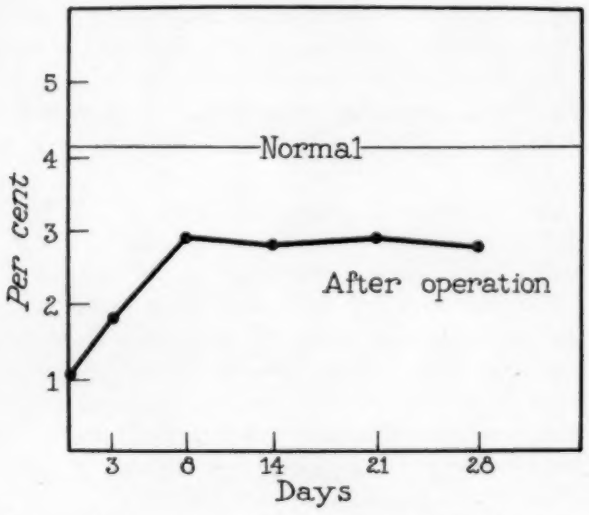

Fig. 3.—The graph shows the weight of liver after operation. The percentage of total weight was due to hepatic tissue at various periods after operation. After the eighth day, there was very little.

that in those rats with large collateral vessels restoration was definitely retarded. Likewise, large collateral vessels were coincident with loss of body weight. Conversely, the lack of collateral vessels was paralleled by increase in weight of liver, and in total weight as well. Thus, large collateral veins were taken as *prima facie* evidence of successful partial obliteration of the portal vein, and in such animals the ratio of the weight of the liver to the weight of the body was uniformly low.

The veins that developed after operation were usually most noticeable in the omentum, part of which was always found adherent to the abdominal wall at the operative scar (fig. 1). These collateral veins

were often larger than the normal portal vein, and were accompanied by smaller veins running up along the esophagus and in the adhesions usually found between the duodenum and the free edge of the liver.

In a few of the animals, the abdominal veins were grossly visible through the wall of the abdomen, but if the omental collateral vessels were large, transillumination disclosed many large vessels. Ascites was never found in an uncomplicated case, although occasionally at necropsy of an animal that had died from peritonitis, free fluid was found in the abdomen.

The cytologic changes were of interest during this period of restoration. In the normal rat, the capsule of the liver was usually thin, and the lobules were fairly large. Central lobular veins were about two or three for each low power field, and each lobule was surrounded by one or two distinguishable peripheral triads consisting of radicles of the portal vein, hepatic artery and biliary duct. The cells of the liver were regular, or polyhedral; they averaged about 20 microns in diameter, with a definite cell membrane and a homogeneous cytoplasm. The nuclei were about 8 microns in diameter, and each contained from one to three nucleoli.

On the third day after operation, the capsule of the liver was somewhat inflamed, being thicker and containing a few invading leukocytes. Central veins and peripheral triads were more prominent, averaging one more for each low power field than the normal, and the hepatic cells were larger, measuring about 24 microns. Their regular polyhedral outlines were lost, and the cytoplasm was definitely vacuolated. This was probably "cloudy swelling," for the most part, but there certainly was actual degeneration near the center of most of the lobules. The sinusoids were large and irregular near the central vein, but almost indistinguishable at the periphery of each lobule.

At the end of eight days, restoration had occurred to some extent, and conditions were almost normal. The cells near the central veins were irregular and had vesicular cytoplasm and small, deeply staining nuclei. The sinusoids were wider at the center of the lobule than at the periphery, but the picture might well be mistaken for the normal. These observations correspond with those reported by Milne.[7]

At two weeks and after, the only difference from the normal was in the vesicular character of the hepatic cells about the central veins. In the third and fourth weeks, some mitotic figures were seen in the parenchymal cells.

COMMENT

Although the results of these experiments seem to indicate that decreased portal blood supply may retard the restoration of the rat's liver after partial hepatectomy, it must not be assumed that this factor

7. Milne, L. S.: J. Path. & Bact. **13**:127, 1909.

alone is responsible. It would strengthen such a conviction, however, if the problem were reversed and hypertrophy of the liver produced by establishment of active congestion through increased blood supply to the organ alone. This has not been done in rats because of technical difficulties, but Higgins [8] has mentioned that hypertrophy of the liver of a chicken was observed following ligation of the vena cava above the kidney, which caused a reversal of flow in the renal portal system and induced a distinct increase in the amount of portal blood reaching the liver.

Whether the amount of blood supplied to the liver through the hepatic artery bears any relation to the ability of the liver to regenerate following injury seems highly speculative. This has not been approached experimentally so far as is known, but this source of supply is so insig-

Averages and Ratios of Weight of Body and of Liver After Partial Hepatectomy and Partial Portal Ligation

Group	Total Weight, Gm.	Weight of Liver at Operation, Gm.				Interval	Weight of liver When Animals Were Killed, Gm.					Change of Weight of Liver		
		By Formula	Removed	Remaining			Total Weight	By Formula	Measured	Per Cent of Normal	Ratio	Total	From Preoperative Weight	From Postoperative Weight	Per Cent
				Grams	Ratio										
8	419.96	6.23	4.31	1.92	0.0127	3	146.57	6.07	2.80	46	0.0190	— 3.39	—3.44	0.88	146
10	126.38	5.03	3.88	1.15	0.0091	8	123.72	4.88	3.53	72	0.0289	— 2.66	—1.50	2.38	306
10	124.64	4.93	3.86	1.07	0.0085	14	110.06	4.20	3.19	76	0.0281	—14.58	—1.74	2.07	296
8	120.10	4.73	3.46	1.27	0.0105	21	111.34	4.27	3.27	74	0.0288	— 8.76	—1.46	2.00	257
5	153.96	6.46	4.04	2.42	0.0157	28	147.98	6.14	4.16	67	0.0278	— 5.98	—2.30	1.74	171
41	135.00	5.47	3.90	1.56	0.0113		Averages								

nificant relatively that it does not prevent atrophy when the portal branches are ligated.

Qualitative studies of the portal blood in the liver following partial ligation of the portal vein have not been made, and I do not know how far certain hypothetic changes in the oxygenation of the tissues and decreased rates of flow may account for the results. However, it seems difficult to believe that any appreciable effect has been induced by such qualitative changes (if they exist), as the hepatic artery had supplied its full quota of blood to the organ.

Assuming that the amount of portal blood reaching the liver was mainly responsible for the reduced restoration following partial removal, how does that fact apply clinically? It may be that these observations explain, in part, the difference between the so-called portal cirrhosis and those degenerative processes that have been grouped together under the term acute atrophy. In both conditions, large quantities of hepatic

8. Higgins, G. M.: Anat. Rec. (supp.) **48**:21, 1931.

tissue are affected, yet if death does not follow the acute destruction, the cirrhosis becomes progressive, and the atrophy usually ends by restoration, both physical and functional. In portal cirrhosis, the degenerative process is mainly about the portal radicles, and the fibrous tissue laid down in the process of repair must seriously impair the blood supply to the surrounding hepatic tissue, even from the first. In the presence of atrophy, however, the blood supply is adequate, and if the original injury has not been too great, and if the injuring agent is removed, complete restoration is the rule.

Observations of the effect of diverting part of the portal blood from the liver on the general weight of the body are of interest in the light of the clinical picture of hepatic infantilism, in which impaired development is explained on the basis of hepatic insufficiency. Although the livers in the rats seemed normal after operation, it is possible that the shunting of the blood through an artificial Eck fistula upset the bodily economy so that vital functions of growth were impeded.

SUMMARY

By combining partial hepatectomy with partial ligation of the portal vein in white rats, it has been possible to prevent, to some extent, the restoration that follows simple partial removal of the liver.

The livers of a series of forty-one rats studied over a period of four weeks did not return to more than 76 per cent of the expected weight, and the weights of the bodies of the animals were continuously below the preoperative level.

Although some of the degenerative and regenerative changes reported by others as following simple partial hepatectomy were observed, these changes were not so marked after this combined operative procedure.

EXPERIMENTAL PATHOLOGY OF THE LIVER

X. RESTORATION OF THE LIVER OF THE DOMESTIC FOWL

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AND
JAMES T. PRIESTLEY, M.D.
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The biologic factors that control the rapid restoration of the liver following partial removal of the organ are still imperfectly known. Restoration does not take place from the level of the cut surface, as in lower forms of life following removal of appendages, but results from cellular hypertrophy as well as hyperplasia of the lobes that remain following partial hepatectomy. Does the liver in the mammal recover its preoperative size and volume in response to a demand by the organism for functional hepatic parenchyma? This would appear probable, except for the fact that the volume of the liver in any normal animal is always functionally greater than that actually required. The liver, as shown clinically and pathologically, possesses a wide margin of safety, and there is every indication that an organism may function adequately with a greatly reduced hepatic parenchyma.

Experimentally Whipple and Hooper [1] showed that when in animals the portal blood was diverted from the liver through an Eck fistula into the posterior vena cava, the volume of the liver was reduced to half its normal size, and that, despite the reduction, with proper diet and housing, these animals maintained apparent good health. Mann and Magath [2] found that when 30 per cent of the liver of an animal with an Eck fistula was removed, the remaining portion remained unchanged, and there was essentially no restoration, and that even with this additional loss of hepatic parenchyma the animals remained apparently normal.

Stephenson [3] found that when he combined partial ligation of the portal vein with partial removal of the liver in the white rat, normal restoration of the organ did not occur. Although he attempted to con-

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From the Division of Experimental Surgery and Pathology, the Mayo Foundation.

1. Whipple, G. H., and Hooper, C. W.: Am. J. Physiol. **42**:544, 1917.
2. Mann, F. C., and Magath, T. B.: Am. J. Physiol. **59**:485, 1922.
3. Stephenson, G. W.: Experimental Pathology of the Liver: IX. Restoration of the Liver Following Partial Hepatectomy and Partial Ligation of the Portal Vein, Arch. Path., this issue, page 484.

strict the portal vein in each animal to a corresponding diameter, it was obviously impossible to deliver equal amounts of blood to the hepatic remnant in every animal. Accordingly, varying amounts of hepatic tissue were restored, but he never encountered more than 76 per cent of the volume that, according to the work of Higgins and Anderson,[4] should develop in response to partial removal alone.

These observations following partial removal of the liver of the dog with Eck fistula, and of the rat after restricting the volume of portal blood entering the liver, indicate the significance of the blood volume as a factor in controlling the extent of hepatic restoration. If the volume of blood that entered a lobe of the liver largely determined the extent of restoration that occurred after partial removal of the organ, then, conversely, an increase of blood delivered to the hepatic remnant should induce an increased amount of new hepatic parenchyma. Accordingly we proposed to test that hypothesis.

The domestic fowl, because of certain vascular arrangements between the systemic and the portal circulation, is an excellent subject on which to determine the effect on the liver of increasing the amount of blood in the portal vein. There is an anastomosis between the inferior mesenteric vein and the iliac veins that lie along, or often embedded within, the kidneys. Thus, through the inferior mesenteric vein, a tributary of the portal vein, there is direct venous continuity between the portal and postcaval vascular systems.

The liver of the fowl is soft and friable in texture and ordinarily comprises two principal lobes, a right and a left, of which the right is considerably the larger. Although the two lobes are connected at their base by a narrow isthmus of hepatic tissue, the left lobe may be easily ligated and surgically removed and the liver thereby reduced to about 60 per cent of its original size. When the left lobe of the liver is removed, restoration of the remaining lobe, to an extent such as takes place in mammals, does not occur. In a large series of hens subjected to the removal of the left lobe of the liver slight restoration did occur, but we have never encountered a restored liver, even after two or three months, with a weight equal to its original preoperative weight. It is our opinion that under these conditions some of the portal blood may have been diverted through the anastomosis of the inferior mesenteric and iliac veins into the posterior vena cava and thereby the volume of portal blood that was delivered to the remaining right lobe of the liver reduced.

The data condensed in this report have been assembled from a series of observations that we have made on the livers of white leghorn cockerels in which we had diverted the blood in the iliac and the femoral

4. Higgins, G. M., and Anderson, R. M.: Arch. Path. **12**:186, 1931.

veins from the posterior vena cava through the anastomosis with the inferior mesenteric vein into the portal vein and thence through the right lobe of the liver.

METHOD OF INVESTIGATION

Forty white leghorn cockerels, aged approximately 6 months and ranging in weight from 1,100 to 1,300 Gm., were used. The flock was divided into three groups, all of which were maintained on the same food and water ration and were housed in laboratory cages under identical laboratory conditions. Five fowls were not operated on, but served as the control group for data on the weight of the liver and the weight of the body during the period of observation. Ten fowls were subjected to partial hepatectomy, in which the left lobe of the liver was removed through a left lateral abdominal incision. Twenty-five fowls were subjected to a two stage operation wherein the posterior vena cava was ligated just anterior to the kidney at the first operation (fig. 1), and two or three weeks later the left lobe of the liver was removed.

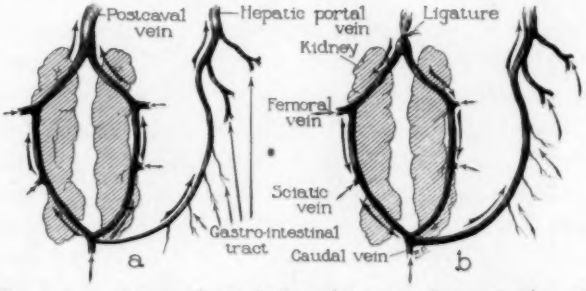

Fig. 1.—In *a*, normal vascular relations between the systemic and the portal circulation in the fowl are shown; in *b*, ligation of the postcaval vein and increased size of the portal system due to diversion of systemic blood.

Of the ten fowls from which the left lobe of the liver was removed, two died as a result of operative difficulties, whereas of the twenty-five subjected to the more difficult procedure of ligating the vena cava, three died during the operation, and nine others died from unknown causes during the ensuing twenty-four hours. Thus eight cockerels with only partial removal of the liver and thirteen with both partial removal and ligation of the posterior vena cava survived the operations, and the data derived from them with those from the control flock are reported. All cockerels were allowed to live for four months after operation and were killed by severing the blood vessels of the neck. All were healthy and had gained in weight; the weights ranged from 1,600 to 2,100 Gm. when the cockerels were killed.

OBSERVATIONS

Although the gross appearance of the restored livers indicated by the sizes of the remaining right lobes was sufficient to convince us that a difference in the extent of restoration had occurred in these two groups of cockerels on which operation had been performed, an analysis of the data from the standpoint of the weight of liver and body is difficult. It is obviously impossible to apply the statistical method, as we did with the

weights of the liver assembled from our study on hepatic restoration in white rats, for the number of fowls is insufficient. It is obviously impossible, too, to gain anything like an adequate estimate of the ratio of the weight of the liver to the weight of the body in this series. Furthermore, such a ratio at the time the fowls were killed would be quite different from that at the time of operation. In order to have accurate indication of the changes in the weight of the liver during the experimental period, it was necessary to know the weight of the liver in a large series of cockerels both at the time of operation and at the conclusion of the experiment. This we have not attempted. We have killed all fowls, however, at corresponding periods following a feeding, so that the changes in the weight of the liver, which pursues a cyclic activity related to feeding,[5] did not enter into our computation. The fowls were weighed just before killing. The livers were removed, all excess blood was drained from them, and they were carefully weighed.

Since the weights of these experimental cockerels when killed varied from 1,600 to 2,100 Gm., we have not attempted to correlate the weight of the liver with the weight of the body. But we have restricted consideration to the weight of the restored liver at the termination of the experiment, and have contrasted it with the estimated weight of the hepatic remnant after partial hepatectomy. Within certain limits of error we have computed the liver component that was removed at operation at 40 per cent of the total liver. This figure, we realize, is subject to error; for although the same lobe was removed in each animal, identical percentages of one lobe in relation to the total liver are not likely to obtain for all individuals. However, for our purposes, it has seemed adequate to estimate the amount of liver that remained within the fowl following partial removal on the basis of the amount removed. Thus, knowing the amount actually removed at operation, we were able to estimate the amount that remained within the peritoneum. Subsequently, when the fowl was killed four months later, the weight of the hepatic remnant subtracted from the final weight of the liver was the amount of liver accepted as the restored portion during the period of observation.

A summary of the data derived from all fowls subjected to partial hepatectomy, but without the ligation of the vena cava, showed that although a considerable amount of hepatic restoration had occurred, the preoperative weight of the liver was not regained. In this first series the average preoperative weight of the liver of the eight cockerels was estimated to be 28.25 Gm. An average of 11.30 Gm. was removed surgically from each fowl, so that 16.95 Gm. of liver was estimated as the average weight of the hepatic parenchyma that remained in the peri-

5. Higgins, G. M.; Berkson, J., and Flock, E.: Proc. Staff Meet., Mayo Clin. **7**:132, 1932.

toneum. At the end of the experiment, four months later, an average weight of liver of 24.67 Gm. was encountered. This is an amount 3.58 Gm. less than the estimated weight of the liver at the time of operation. Although the difference between these two figures is not large, yet in contrast with corresponding observations on mammals it is significant. Furthermore, there was an average increase of 550 Gm. in the weight of the cockerels during this period, so that certain increases in the weight of the liver might well have been anticipated. Some restoration had occurred, and the average increase in the weight of the liver during the four months over the estimated weight of the hepatic remnant following operation was 7.7 Gm., which is an increase of approximately 45 per cent.

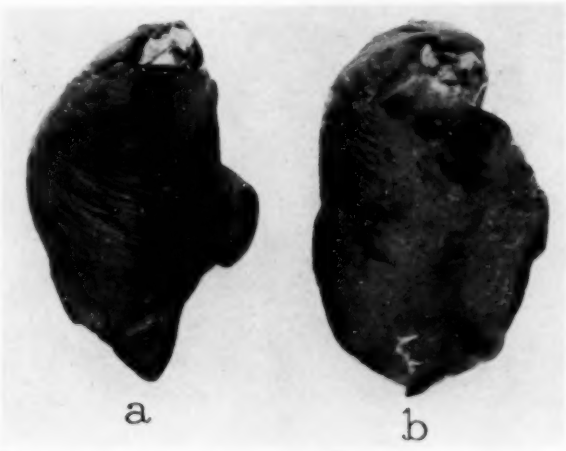

Fig. 2.—In *a* is shown the left lobe of the liver of a cockerel four months after removal of the right lobe; in *b*, left lobe of the liver of a cockerel four months after ligation of the postcaval vein and removal of the right lobe. The increase in size is apparent.

The data assembled from the group of thirteen cockerels in which the posterior vena cava was ligated and the left lobe of the liver removed showed a much greater increase in the extent of restoration of the remaining right lobe (fig. 2). In these cockerels, the inferior mesenteric vein was always from three to four times its usual size, distended by the increased volume of blood coursing from the legs and the kidneys to the portal vein. In this series, an average of 11.2 Gm. of liver was removed from ten days to two weeks after the posterior vena cava had been ligated, leaving an average of 16.78 Gm. of parenchyma within the cavity of the body. After four months, the cockerels were killed, and the average weight of the liver was 29.27 Gm. Since the hepatic remnant at operation was estimated to weigh 16.78 Gm., we conclude that approximately 12.49 Gm. of liver had been produced in each fowl

during the experimental period. In each of the thirteen successful experiments, a liver was encountered at necropsy greater in weight than that estimated present before operation. The average increase in the weight of the liver in these fowls subjected to both operations, in which the systemic blood from the legs and kidneys was shunted through the inferior mesenteric vein into the portal vein, was greater by 4.79 Gm. than that in the weight of the liver in those subjected to partial removal alone. In other words, as far as we were able to secure an accurate analysis of the data, we had induced in these fowls, by the increase in the amount of blood passing through the gland, restored livers approximately 62 per cent greater than in the flock with partial hepatectomy alone.

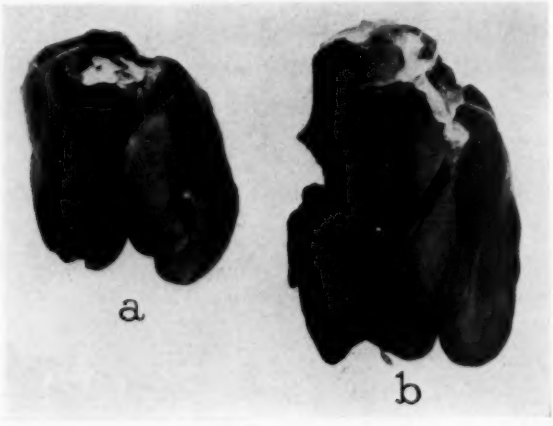

Fig. 3.—In *a* is shown the normal liver of a cockerel; in *b*, liver of a cockerel four months after diverting systemic blood into the portal system.

The relation between the size of the liver and the volume of blood traversing the organ is further indicated by a few observations that we have made on cockerels subjected to an operation in which the posterior vena cava above the kidney was securely ligated. In four fowls, successfully operated on and explored four months later, the livers were very much larger than when seen at operation and larger than those in the controls (fig. 3). It seems probable that the capillary bed in the liver in these fowls was inadequate to handle the increased volume of blood that was delivered to the portal vein, so that an increase in the size and volume of the gland resulted. We have not attempted to correlate the increase in the size of the gland with the increase in the amount of blood coursing through the portal vein, although no doubt the two bear a significant correlation.

There were no significant differences in the histologic appearance of these restored livers, and they were essentially like the livers from the

control fowls not operated on. We have not followed the changes that may have occurred in the right lobe of the liver immediately following the operative procedures, but we have studied sections taken from all fowls at the end of the experiment. There was no congestion in the liver that received the added volume of blood, and certainly sections stained with hematoxylin and eosin afforded no criteria that would render identification possible.

COMMENT AND SUMMARY

These results on fowl are wholly in accord with observations hitherto made on the dog and the rat, and substantiate rather definitely the opinion that the volume of blood which is delivered to any hepatic remnant after partial hepatectomy determines largely the extent of its restoration. It seems clear that the rapid restoration of a small portion of the liver to a size even greater than the normal organ, as in rats, is due to responses that are induced by mechanical factors associated with the volume of portal blood traversing the gland. In the cockerel, the degree of restoration after removal of the left lobe only was far less in proportion to that which occurs in the mammal, and it is our opinion that a considerable quantity of the blood that drains the gastro-intestinal tract passed through the anastomosis between the inferior mesenteric vein and the iliac veins to the posterior cava. When the systemic blood from the legs and back was delivered to the portal vein by ligation of the posterior vena cava just anterior to the kidney, the size of the remaining right lobe, after removal of the left, was greater in four months than the normal liver on which operation had not been performed.

HEMATOPOIETIC EFFECT OF NUCLEAR EXTRACTIVES OBTAINED FROM RED BLOOD CELLS OF THE FOWL

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In 1926, we published [1] the observation that when nucleated red blood cells of the fowl (chicken and duck) were introduced into the blood stream of the rabbit, a marked increase in the number of the erythrocytes and in that of the leukocytes, as well as in the percentage of hemoglobin, occurred. The intravenous injection of washed nuclei from chicken blood cells produced the same effect; but the injection of the cell stroma—the hemoglobin-bearing portion of the cell—obtained from the horse and the dog did not produce this effect. The injection of nuclear extractives in the form of the sodium salts of nucleic acid and nucleoproteins obtained from chicken blood cells was followed by a like response.

In subsequent papers,[2] we reported experimental and clinical data on the effect of nuclear extractives obtained by the methods of Kossel-Neumann [3] and Hammarsten [4] from the liver, spleen, pancreas and heart of the beef, the thymus of the calf, the kidney, liver and stomach of the hog, and the liver of the salmon, when given by mouth to anemic dogs and to patients suffering from both primary and secondary forms of anemia. It was shown that an active hematopoietic response to the feeding of these substances took place within a few days, as shown by a rapid increase in the reticulocyte count, which was followed immediately by an increase in the erythrocyte count and in the hemoglobin content.

In the present paper, we give further data on the hematopoietic effect of nuclear extractives from chicken blood cells, obtained by the

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1. Arch. Path. **2**:698, 1926.

2. J. A. M. A. **89**:682, 1927.

3. Mathews, A. P.: Physiological Chemistry, ed. 5, New York, William Wood & Company, 1930, p. 169.

4. Text Book of Physiological Chemistry, ed. 6, edited by Mandel, New York, John Wiley & Sons, 1911.

aforementioned methods, when fed to dogs with controlled experimental anemia.

METHODS

Anemia in which the hemoglobin content of the red cells was roughly 50 per cent, was produced and maintained in five dogs after the method of Whipple and Robscheit-Robbins.[5] On these anemic dogs, we conducted a series of eight experiments during a period of eighteen months in order to determine the amount of hematopoietic stimulation, if any, produced by the administration of nuclear extractives obtained from chicken blood cells. The authors mentioned had demonstrated

TABLE 1.—*Series 1, Dog 1*

Date	Weight, Kg.	Plasma Volume, Cc.	Blood Volume, Cc.	Cell Volume, Cc.	Hemoglobin, per Cent	Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions	Reticulocytes, per Cent	Withdrawn Blood, Cc.	Withdrawn Hemoglobin, Gm.
1/12/30	30.0	479	874	395	....	14.8	5.76	...	...	6.6
1/26/30	30.0	576	952	376	....	14.2	5.77	...	...	5.1
2/ 2/30	30.0	...	...	...	82.6	14.4	....	...	246	34.0
2/ 9/30	26.5	...	...	...	74.3	10.25	....	...	130	13.3
2/16/30	26.0	...	...	...	77.4	10.68	....	...	268	28.4
2/23/30	27.0	...	...	...	66.0	9.11	....	...	320	29.2
3/ 2/30	26.0	...	...	...	54.6	7.54	....	...	116	9.8
3/ 9/30	24.0	...	...	...	45.7	6.31	....	...	10	0.6
3/16/30	23.0	447	680	233	49.6	6.83	3.53	...	46	3.07
3/23/30*	23.0	...	...	...	44.4	6.10	3.91	...	10	0.6
3/30/30	22.2	...	...	...	71.4	9.86	5.42	...	200	19.7
4/ 7/30	23.4	...	715	...	85.4	10.11	5.80	...	234	23.4
4/13/30	22.2	...	...	...	78.4	8.56	5.74	...	185	15.3
4/20/30	22.7	...	664	...	89.8	9.81	....	...	160	14.2
4/27/30	23.5	448	640	192	72.3	9.9	4.92	...	200	19.2
5/ 3/30	24.0	...	690	...	72.7	10.04	4.68	...	200	20.08
5/11/30	24.2	...	...	...	58.4	8.03	....	1.0	100	8.03
5/18/30	24.2	...	...	...	61.7	8.50	4.79	0.6	10	0.85
5/25/30*	24.2	...	...	...	61.6	8.5	4.00	0.2	150	12.04
6/ 1/30	24.5	...	...	...	51.2	7.06	5.20	6.0	10	0.76
6/ 7/30	25.2	(Dog died)	...	...	74.6	10.3	6.52	5.6	200	21.0

* Ten grams of nuclear extractives was added to the diet from March 23 to April 20 and from May 25 to June 7, 1930.

in their experimental work that the amount of hemoglobin regenerated in the body can be modified at will by control of the diet. We verified this conclusion in our experiments. In order to insure a constant stimulus to the production of hemoglobin and red blood cells, we maintained for these animals throughout a routine diet that contained ample quantities of all the food elements essential for normal growth, nutrition and health with a minimum of blood-forming materials.[5] By means of a series of frequent bleedings of calculated amounts we maintained a severe secondary anemia with a hemoglobin level about 50 per cent of normal. The samples of blood removed were measured each time for total hemoglobin, and we estimated from week to week the amount of hemoglobin each animal could produce under the standard

5. Am. J. Physiol. **72**:395, 1925.

controlled conditions of diet, room temperature, cleanliness, contentment and exercise. We assumed that under these conditions, with a hemoglobin level kept at approximately 50 per cent of normal, the stimulus to hemoglobin and red blood cell formation was a sustained maximum, and therefore should test the value of any diet or therapeutic agent used for hematopoietic stimulation.

The dog was chosen as an experimental animal because its hematopoietic system is relatively stable and because it is large, easily trained, and friendly (factors that aid in maintaining maximum accuracy of technic) and because it is a good feeder, is hardy and keeps healthy despite prolonged severe anemia. Each dog was kept in a separate, well

TABLE 2.—*Series 1, Dog 2*

Date	Weight, Kg.	Plasma Volume, Cc.	Blood Volume, Cc.	Cell Volume, Cc.	Hemoglobin, per Cent	Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions	Reticulocytes, per Cent	Withdrawn Blood, Cc.	Withdrawn Hemoglobin, Gm.
1/12/30	22	406	815	409	131.6	18.15	5.86	...	105	18.16
3/16/30	24	555	875	320	72.5	7.35	4.85	...	230	16.90
4/ 6/30	23	...	765	...	74.6	8.8	....	...	148	16.3
4/13/30	23	...	...	...	72.0	9.95	4.39	...	234	23.3
4/20/30	25	...	663	...	69.0	9.52	....	...	155	13.0
4/27/30*	26	575	736	161	52.0	7.13	3.98	0.8	43	3.1
5/ 4/30	27	...	...	...	58.8	8.25	5.34	5.0	8	0.7
5/11/30	28	692	932	240	61.0	8.42	....	...	60	5.05
5/18/30	28	...	...	...	81.6	11.26	7.46	...	258	29.0
5/25/30	28	...	...	...	75.1	10.35	5.2	1.2	233	24.1
6/ 1/30	28	...	...	...	52.8	7.29	4.9	...	8	0.6
6/16/30	30	...	...	...	70.0	9.2	5.2	0.8	92	8.5
6/23/30*	29	522	710	188	60.0	8.2	4.2	0.5	8	0.6
6/26/30	..	...	...	...	....	....	5.06	6.0	...	....
6/29/30	..	...	...	...	80.5	11.6	7.10	4.6	157	18.5

* Ten grams of nuclear extractives was added to the diet from April 27 to May 18 and from June 23 to June 29.

ventilated, warm, clean compartment of the kennel. It was fed a weighed amount of the standard diet once daily, was given water at all times and was exercised daily.

After the dogs were accustomed to their surroundings, we determined in each one the normal blood plasma volume and cell volume, the red blood cell count, the percentage of reticulocytes, the percentage of hemoglobin, the grams of hemoglobin per hundred cubic centimeters of blood and the body weight. These normal calculations were checked and rechecked before inducing anemia. The blood volumes were obtained by the method of Hooper, Smith, Belt and Whipple.[6] Our results checked well, and we became satisfied with the accuracy of the method. For the determination of the percentage of hemoglobin and the grams of hemoglobin per hundred cubic centimeters of blood, we

6. Am. J. Physiol. **51**:205, 1920.

followed the method of Osgood and Haskins.[7] Twenty estimations by this method on one sample of blood, each estimation being checked by at least two observers, gave a percentage of error of not to exceed 1 per cent. The red blood cell counts were made with oxalated venous blood,

TABLE 3.—*Series 1, Dog 3*

Date	Weight, Kg.	Plasma Volume, Cc.	Blood Volume, Cc.	Cell Volume, Cc.	Hemoglobin, per Cent	Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions	Reticulocytes, per Cent	Withdrawn Blood, Cc.	Withdrawn Hemoglobin, Gm.
1/12/30	21.0	463	891	428	91.6	15.9	5.76	...	...	....
1/26/30	25.0	...	...	...	....	14.4	6.02	...	45	5.14
2/ 9/30	26.0	...	...	...	96.7	13.36	....	...	300	40.5
2/16/30	28.0	...	...	...	86.2	11.9	....	...	126	14.9
2/23/30	24.0	...	...	...	59.9	8.25	....	...	220	18.2
3/ 2/30	24.0	...	...	...	59.8	8.25	....	...	200	16.5
3/ 9/30	23.7	...	...	...	60.3	8.32	4.05	...	205	17.1
3/16/30	24.0	366	526	160	56.9	7.85	3.38	...	190	14.3
3/23/30*	23.0	...	...	...	49.3	6.8	3.18	...	...	0.7
3/30/30	22.5	...	...	...	97.6	13.46	5.86	10.3	260	33.2
4/ 7/30	23.5	...	825	...	84.5	12.42	4.64	...	266	27.8
4/13/30	24.0	...	706	...	69.4	8.42	....	...	150	12.55
4/20/30	24.0	...	860	...	64.7	7.86	3.32	...	100	7.86
4/27/30	24.0	564	693	129	....	7.92	3.5	...	50	3.5
5/ 4/30	25.0	613	779	166	....	....	3.88	0.8	...	....

* Ten grams of nuclear extractives was added to the diet from March 23 to April 7, 1930.

TABLE 4.—*Series 2, Dog 1*

Date	Weight, Kg.	Plasma Volume, Ce.	Blood Volume, Ce.	Cell Volume, Ce.	Hemoglobin, per Cent	Hemoglobin, Gm. per 100 Ce.	Red Blood Cells, Millions	Reticulocytes, per Cent	Withdrawn Blood, Cc.	Withdrawn Hemoglobin, Gm.
12/ 4/30	30.5	...	...	...	115.3	15.9	6.84	...	62	9.9
12/11/30	29.5	500	1000	500	106.0	14.6	6.25	...	287	42.0
12/16/30	27.0	548	880	332	89.6	12.4	4.45	...	231	30.3
12/30/30	27.5	...	...	...	78.2	10.7	....	...	283	30.5
1/ 1/31	27.0	...	...	...	86.4	11.9	....	...	150	17.9
1/ 8/31	25.0	...	...	...	93.3	12.9	....	...	295	38.0
1/13/31	28.0	...	...	...	78.35	10.8	....	...	218	23.6
1/20/31	27.5	...	...	...	82.7	11.4	....	1.7	295	33.6
1/27/31	27.5	...	...	...	87.9	12.1	4.51	...	274	33.2
2/ 3/31	27.5	...	750	...	71.8	9.9	4.15	...	228	22.6
2/10/31	28.0	...	...	...	69.1	9.5	2.94	...	175	16.67
2/17/31*	28.0	...	...	...	50.3	6.9	2.99	0.9	50	3.5
2/24/31	27.0	...	...	...	78.9	10.84	5.13	...	240	25.2
3/ 3/31	28.5	451	670	119	83.8	11.55	6.1	15.0	207	24.0
3/10/31	28.5	...	...	...	78.9	10.9	5.99	...	215	23.4
3/17/31	27.5	...	...	...	73.35	10.1	5.7	8.0	240	24.2
3/24/31	28.0	...	...	...	91.3	12.6	8.62	...	318	41.0
4/ 5/31	28.5	...	...	...	72.4	10.0	....	...	215	21.5

* Ten grams of nuclear extractives was added to the diet from Feb. 17 to March 19, 1931.

with the standard technic and the improved Neubauer hematocytometer calibrated for research work. The percentage of reticulocytes and the total number of reticulated red blood cells per cubic millimeter of blood were obtained by using brilliant cresyl blue and a light counterstaining with Wright's stain.

7. Osgood, E. E., and Haskins, H. D.: A Textbook of Laboratory Diagnosis with Clinical Applications for Practitioners and Students, P. Blakiston's Son & Co., 1931, p. 347.

The dogs were bled once each week. Before each bleeding we estimated the blood volume of the dog and the grams of hemoglobin per hundred cubic centimeters of blood, from which we calculated the amount of hemoglobin necessary to be removed in order that the total hemoglobin in grams left in each animal should equal 50 per cent of the original normal. Sufficient blood was then removed to leave the animal with one half of its original hemoglobin as estimated in grams. Never, however, did we remove more than one third of the total volume of blood, and usually three or four bleedings were necessary to reach a 50 per cent hemoglobin level. For approximately two months the

TABLE 5.—*Series 2, Dog 2*

Date	Weight, Kg.	Plasma Volume, Cc.	Blood Volume, Cc.	Cell Volume, Cc.	Hemoglobin, per Cent	Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Millions	Reticulocytes, per Cent	Withdrawn Blood, Cc.	Withdrawn Hemoglobin, Gm.
12/16/30	29.0	...	...	...	116.0	16.05	6.75	...	35	5.6
12/20/30	27.5	604	1160	556	107.7	14.8	....	...	318	47.2
1/ 1/31	28.0	...	...	...	85.8	11.85	....	...	285	33.7
1/ 8/31	25.5	...	...	...	93.0	12.90	....	...	290	37.3
1/13/31	30.0	...	...	...	75.7	10.4	....	...	218	28.9
1/20/31	28.5	...	...	...	72.8	10.1	....	...	318	32.0
1/27/31	27.5	...	...	...	80.4	11.1	3.82	...	281	31.8
2/ 3/31	26.5	...	834	...	66.9	9.10	3.48	...	165	16.7
2/10/31	25.0	...	...	...	69.0	9.60	3.05	...	100	9.6
2/17/31*	24.5	...	...	...	58.10	8.00	3.51	...	40	3.2
2/24/31	24.5	...	...	...	84.90	11.70	5.92	1.1	240	28.1
3/ 3/31	25.0	...	...	...	69.10	9.50	5.40	4.0	260	24.8
3/10/31	26.5	500	750	250	69.9	9.65	6.40	...	250	24.2
3/17/31	26.5	...	...	...	73.6	10.2	5.90	...	258	26.2
3/24/31	25.5	...	...	...	77.0	10.6	6.55	1.2	270	27.7
4/ 7/31	25.0	...	...	...	74.3	10.2	....	...	285	29.4
4/21/31	25.0	...	...	...	77.0	10.2	....	...	235	25.0
4/29/31*	25.0	550	755	196	78.3	10.8	3.85	...	200	21.6
5/ 5/31	27.0	...	...	...	84.6	11.7	6.09	5.5	300	42.0
5/15/31	28.0	...	...	...	96.2	13.3	....	...	325	43.2
5/19/31	28.4	...	...	...	73.6	10.25	6.11	7.1	335	34.34

* Ten grams of nuclear extractives was added to the diet from Feb. 17 to March 10 and from April 29 to May 19, 1931.

weekly regeneration of hemoglobin was astonishingly great; it often equaled one fourth of the amount of the original total hemoglobin. With each bleeding the regenerated hemoglobin, however, became less, so that after from ten to twelve weeks it remained comparatively small. We were obtaining, therefore, at this point the maximum stimulus to the production of hemoglobin from the diet; all the reserve hematopoietic materials had been exhausted by the repeated losses of blood.

The different animals responded differently to the bleedings, both as to regeneration of hemoglobin and as to the time needed to deplete the body of reserve hematopoietic materials, but on the whole the ultimate results were satisfactory. After maintaining a constantly severe secondary anemia with the maximum hematopoietc stimulation possible from the diet used and with a minimum amount of hemoglobin

regenerated weekly, we added to the diet daily 10 Gm. of the nuclear extractives obtained from the red corpuscles of chicken blood.

OBSERVATIONS

When the regeneration of hemoglobin was less than 6 Gm. per week, we considered the anemic animal satisfactory for experimental use. The average total amount of hemoglobin in our normal dogs was 152 Gm., with a low content of 146 Gm. and a high content of 162. The total content of hemoglobin in the anemic dogs was between 50 and 60 Gm. After the addition of 10 Gm. of nuclear extractives daily to the diet, the dogs regenerated from 23 to 29 Gm. of hemoglobin each week, whereas, on the standard diet alone, they regenerated less than 6 Gm. in

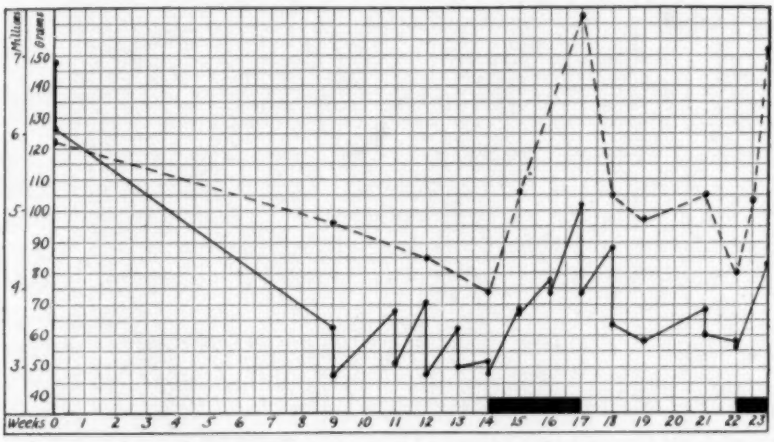

Chart 1.—The solid line represents estimated total hemoglobin in grams, based on percentage of hemoglobin and grams of hemoglobin per hundred cubic centimeters of blood at the time of the different readings. The horizontal continuation of this line represents time in weeks (two spaces per week). The vertical variation represents changes in the amount of hemoglobin. The vertical sections of the line between two points of the same week represent withdrawals of blood, one space representing 5 Gm. of hemoglobin. The broken line represents the red blood cell count. The weekly counts made during the preliminary stages of bleeding are not indicated, giving the unbroken descent of this portion of the graph. Red blood cell counts after the amount of hemoglobin was sufficiently reduced are indicated weekly with the estimations of hemoglobin. The heavy blocks of black indicate periods during which nuclear extractive was added, in the amount of 10 Gm. daily, to the regular diet. In chart 1, the hemoglobin curve and the curve of the red blood cell count of dog 2, series 1, are shown.

the same period of time. We noted, too, that for three or four weeks following the withdrawal of the nuclear extractives from the diet the dogs continued to regenerate from 18 to 20 Gm. of hemoglobin each week, indicating not only that the extractives were capable of stimulat-

ing an immediate production of hemoglobin, but also that an amount of the stimulant was stored in the animal's body sufficient to maintain regeneration for from three to four weeks longer. We noted further that if the extractives were again administered before depletion of the stimulant had occurred, the animal responded at once by a greater production of hemoglobin than had taken place in the beginning. For example, dog 2, series 2, regenerated 29, 25 and 21 Gm. of hemoglobin, respectively, during three successive weeks following the omission of the extractives from the diet, and during the fourth week, on 10 Gm. of the extractives daily, regenerated 42 Gm. of hemoglobin. The accompanying tables give the details of the experiments.

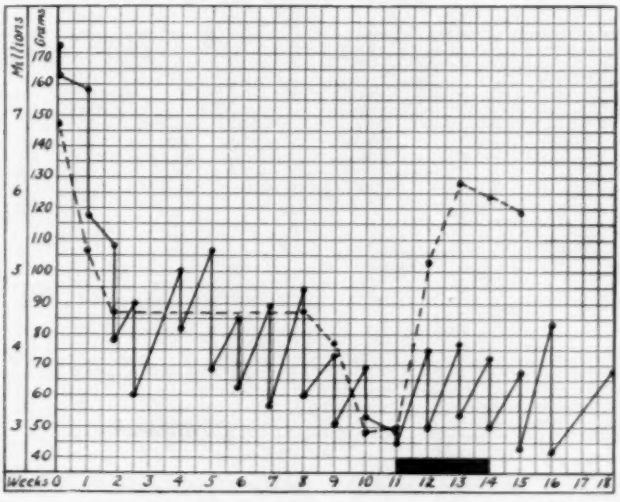

Chart 2.—The hemoglobin curve and the curve of the red blood cell count of dog 1, series 2. See legend of chart 1 for further explanation.

COMMENT

The problem of the effect of nuclear extractives obtained from the red blood cells of the fowl began in 1924 as a histologic study of the fate of the whole blood cells when introduced into the blood stream of the rabbit. The animals surviving the initial shock of the blood transfusion showed uniformly profound hematopoietic stimulation. The red blood cell count increased in certain instances from 32 to 55 per cent above the normal and remained elevated for periods of weeks. It was found that the stroma of the cell did not produce this effect, but that washed nuclei obtained from the cells did, and that nucleoproteins and sodium salts of nucleic acids possessed the same properties. Administration of the latter extractives was made at first by intravenous

injection, both into normal rabbits and dogs and into patients suffering from pernicious anemia and different forms of secondary anemia. Hematopoietic stimulation was observed in both instances, but the patients frequently suffered anaphylactic-like shock, possibly from lack of refinement of the product, and this method was therefore replaced by oral feeding. The making of the extractives from chicken blood cells in sufficient quantity to continue experimentation proved to be impractical, and because the unknown factor causing the hematopoietic effect seemed to be confined to the nucleus, extractives were obtained by the same methods from the various glandular organs mentioned. These extractives were studied in the same manner as those from the chicken blood cells, with the result that the same hematopoietic effect was obtained in each instance, and this effect seemed to be roughly proportional to the amount of nuclear extractives in the several organs.

As many factors may enter into the composition of animal fractions obtained from liver, kidney, stomach, etc., the present study of extractives from the red blood cells of the fowl, from which extraneous factors were automatically eliminated, was planned. A sufficient quantity of the material was prepared to permit the experimental work described and also to treat clinically a few patients with pernicious anemia. Thus far three such patients have been treated for a sufficient length of time to recognize the same response in reticulocyte count, red blood cell count and hemoglobin content that follows the proper administration of liver or stomach extractives available in the market. The records of these patients will be published elsewhere.

SUMMARY

The hematopoietic response in a series of five dogs with severe anemia, produced by periodic bleedings and controlled by a standard diet, to the daily oral administration of 10 Gm. of nuclear extractives from the nucleated red blood cells of the fowl has been studied eight times.

The response to the feeding of these extractives consists of a sharp rise in the percentage of reticulated red blood cells, an increase in the red blood cell count and a corresponding increase in the percentage and volume of the hemoglobin content.

As no other factors that may influence regeneration of the blood have entered into these controlled experiments, it is permissible to conclude that a factor exists within the nucleus of the red blood cell of the fowl which has the power to stimulate markedly the production of blood in the dog.

From these results and from other experimental work previously reported by us it is reasonable to conclude that this hematopoietic stimulant is common to the nuclei of many tissue cells.

Laboratory Methods and Technical Notes

AN AUTOPSY TABLE—A NEW DESIGN

WILEY D. FORBUS, M.D., DURHAM, N. C.

If one is confronted by the problem of equipping an autopsy room, two views of the situation may be taken. One may look on it as just another equipment problem the solution of which is to be found in the catalogue of any one of a number of manufacturers merely by turning to the index, a problem requiring little thought and deserving less, since, after all, it may be said that essentially one needs only a cramped cellar room, a pair of carpenter's horses and two boards, a pair of scissors, a saw and a butcher's knife. On the other hand, the problem may be considered worthy of some deliberation, especially since the autopsy room can be made a place where more than pathologic anatomy may be taught.

I have found justification for the second attitude toward the problem in the following reasonably sensible propositions.

First of all, good autopsy technic is a sine qua non of postmortem investigation of disease. Without this, the procedure is of little value and in a large number of instances actually harmful, since poor technic reflects discredit on a fundamentally unassailable method of investigation of disease.

In the second place, good technic cannot be taught or insisted on without at least reasonably convenient equipment.

The third proposition is that all clinicians are by nature repelled (and not infrequently justifiably so) by the autopsy, which they look on as a ghastly procedure that they are more than happy to leave to the pathologist, in spite of the element of necessity for the common good which they recognize in the procedure.

The fourth and last proposition is, therefore, that it is to the distinct advantage of all parties concerned that the autopsy be done in the neatest, cleanest manner, and that everything done shall be with due regard for common sensibilities. The autopsy room should, therefore, be so located and so equipped that it will attract and not repel.

Thus guided, I have given some thought to the planning of an autopsy table. To a large degree I have been forced to do this by the obvious inadequacies of the various tables offered by the manufacturers, both domestic and foreign, and by the desire to conserve the equipment funds of my department. The table which I have designed has been in use for about two years and has proved eminently satisfactory from every essential point of view. It was constructed partly by manufacturers in Baltimore and partly in the shop of Duke University. The details and specifications are as follows:

From the Department of Pathology, Duke University School of Medicine.

SPECIFICATIONS FOR AUTOPSY TABLE

Table Top.—1. The top (figs. 1 and 2) is made from a slab of white marble 4 by 30 by 94 inches (10.16 by 76.20 by 238.76 cm.).

2. The surface is countersunk according to the measurements given in figure 3 *B*, allowing for a rim or margin of 1½ inches (3.77 cm.) of thickness.

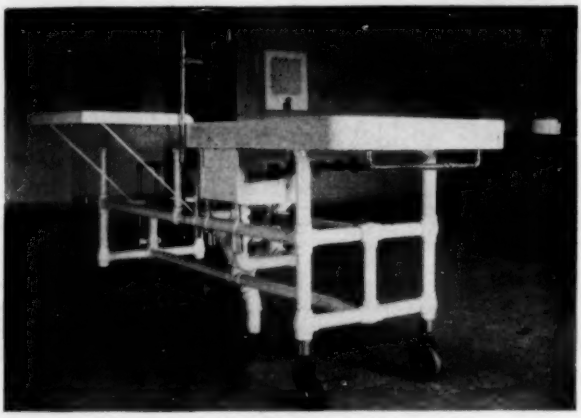

Fig. 1.—Autopsy table, showing the small sink, the valves in the water supply lines and the detachable side table.

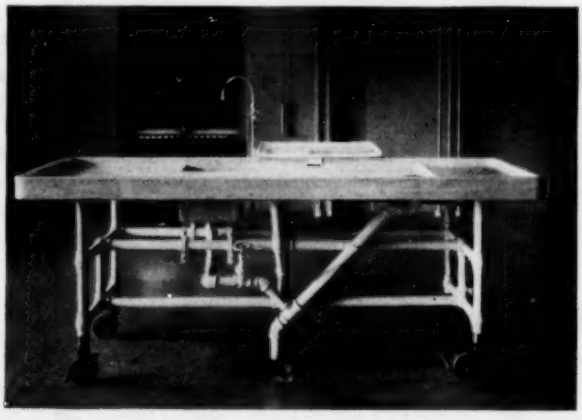

Fig. 2.—Autopsy table, showing the plan of the marble top.

3. The surface is graded in such a way that all drainage falls toward the main drain pipe near the foot of the table, as shown in figure 3 *B*. From the head to the main drain there should be a fall of at least ¾ inch (1.83 cm.). In addition to this there should be a fall from the extreme sides to the center (fig. 3 *C*) of at least ¼ inch (0.61 cm.).

4. As will be seen in figure 3 *B*, the foot of the table consists of a shelf, the surface of which is 1 inch (2.5 cm.) above the surface of the table at the line of

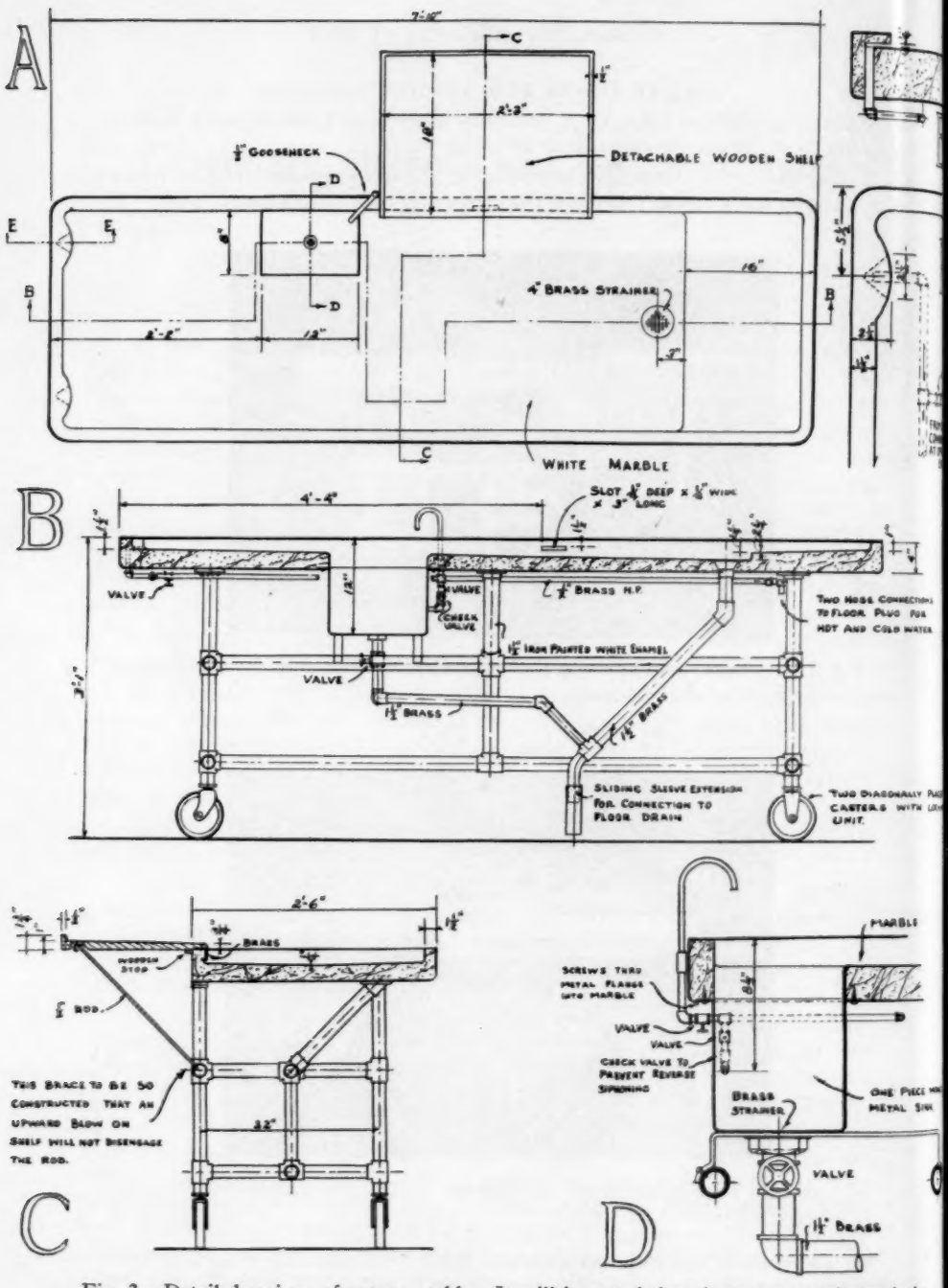

Fig. 3.—Detail drawings of autopsy table. It will be noted that there are certain variations between the specifications, the photographs and the drawings; the drawings have been made to show the more recent changes and improvements that have been made since the original table, shown in the photographs, was constructed. *A* is the top view plan. The lines B-B, C-C, D-D and E-E shown in this view indicate the sections the plans of which are shown in *B*, *C*, *D* and *E*. *F* shows the plumbing detail at *E*.

junction of the two. This shelf is also graded, the fall from the foot to its edge, just below the main drain grid, being ¼ inch (0.61 cm.). No grade from the sides of this shelf to the midline is necessary.

5. Twenty-four and a half inches (62.23 cm.) from the head of the table (inside measurement), a 12 by 8 inch (30.48 by 20.32 cm.) block of the table top is cut out, the outer margin of this opening being formed by the 1½ inch (3.77 cm.) margin of the table (fig. 3 *D*).

6. At the head of the table, the top is bored with openings for two water inlet pipes, the details of which are shown in figure 3 *E* and *F*, and the locations of which are seen in the top view (fig. 3 *A*). The width of the rim at the location of these openings is increased to 2½ inches (6.27 cm.) for reinforcement. Water flows on the table from these pipes through a fan-shaped opening in the marble rim. See figure 3 *F*.

7. At the foot of the main part of the table in the midline is placed an opening through which passes a 1¾ inch (4.33 cm.) drain pipe. Over this opening and countersunk, flush with the surface, is placed a brass strainer of ¼ inch (0.61 cm.) mesh and of 4 inch (10.16 cm.) diameter.

8. Into the left side of the table top—that is, the inner surface of the left margin—52 inches (132.1 cm.) in over-all measurement from the head of the table, is carved a rectangular groove 3 by ¼ by ¼ inches (7.6 by 0.61 by 0.61 cm.), details of which are shown in figure 3 *B*.

9. The table top is attached securely to the upright posts of a cast-iron pipe frame, on which it is mounted by screws that pass through the capitals and into the under-surface of the marble. The openings for these screws should not pass through the slab.

10. On the under-surface of the table exactly in the middle and extending from head to foot is attached a ¾ inch (1.83 cm.) water-pipe by means of brackets attached to the marble by screws. At the head end, 3 inches (7.6 cm.) from the edge, the water-pipe divides forming a "T" to supply water to the two outlets near the corners of the table (fig. 3 *F*). The water-pipe is connected to two supply lines, one for hot and one for cold water (located in a floor plate), by means of rubber hose. Openings in the under-surface of the marble in pairs to accommodate screws for the attachment of this water-pipe are located at intervals of 24 inches (60.96 cm.). These openings should not go through the slab.

On the left side of the table, 39 inches (98.50 cm.) from the head (over-all measurement) is located a pair of openings into the outer surface of the margin to accommodate two screws for the attachment of a bracket to secure a goose-neck water outlet, as shown in figure 3 *D*.

11. About the margin of the cut-out in the table top on the under-surface of the table there is a rectangular groove ¼ inch (0.61 cm.) deep and 1 inch (2.5 cm.) wide, into which fit the flanges of a sink which is located beneath the table and attached by means of screws passing through the flanges and into the slab from beneath (fig. 3 *D*). Screw slots are made in the marble for this attachment, two pairs on each side and one pair at each end.

12. All corners throughout are rounded.

Base of the Table.—1. The table top is mounted on an iron pipe frame, all surfaces of which are covered with white enamel paint. The measurements and general plan of construction are shown in figure 3 *B* and *C*.

2. It will be noted that the carriage is not the same size as the table top. At the ends, the mount is set back 10 inches (25.4 cm.), and on the right side the carriage posts are set back 6 inches (15.24 cm.). On the left side, however, the edge of the top and that of the mount are coincident.

3. All of the various members of the frame meet at right angles, except the center upright post, which is set at an angle of about 135 degrees. This is arranged to give unobstructed working room beneath the table on this side and to make easily accessible all water connections, etc. See figure 3 *B* and *C*.

4. The four corner posts of the frame are mounted on casters, which should be ball-bearing or roller-bearing and rubber-tired, and two of which, diagonally located, are capable of being locked.

5. The table top is securely fastened to the frame mount by screws that pass through capitals surmounting the six points of support and into the under surface of the marble slab.

Plumbing.—1. Two drain pipes are required, the main one leading from the grid at the foot of the table and the other leading from the bottom and center of the small sink, as shown in figure 3 *B*. These pipes are of brass and should join, the common opening being 2 inches (5 cm.) from the floor and 42 inches (106.68 cm.) from the inner edge of the foot end of the frame support. Both of these drains are fitted with proper joints, so that they can be easily detached for cleansing. The drain from the small sink is guarded by a valve, with the stem pointing to the head of the table about 4 inches (10.16 cm.) below the base of the sink.

2. Water is supplied to the table at four points by branches from a main lead which begins at the foot of the table in the midline. From this point it passes toward the head, giving off one branch that supplies the goose-neck outlet, 39 inches (98.50 cm.) from the head (over-all measurement), and two branches, opposite to each other, 3 inches (7.6 cm.) from the head. The latter two branches penetrate the marble top and end in a splash plate arrangement as shown in figure 3, *E* and *F*.

The fourth point of supply to the table is from a branch of the goose-neck lead, which enters the bottom of the small sink or, if more easily accomplished, from the side of the sink 4 inches (10.16 cm.) below the table top. Four valves should be placed in this system, all under the table: one to control the inlet to the goose-neck, one to control the supply to the small sink, one to control the two outlets at the head of the table and the fourth, a check valve, to prevent reverse flow through the lead supplying the side or bottom of the sink.

All pipes are of nickel-plated brass. The pipes are secured to the under-surface of the table top by brackets and screws.

The connections of the main line of water supply with the hot and cold water lines in the floor are made of rubber hose.

3. For the location, measurements, etc., of the small sink see figure 3. The sink should be made of heavy monel metal. It is held in place by screws that pass through flanges into the marble top (fig. 3 *D*), and is supported on iron bands attached to the upper longitudinal members of the frame support. The connections here must be waterproof. The drain opening is guarded by brass strainers of ¼ inch (0.61 cm.) mesh.

Detachable Side Shelf.—The shelf is made of wood and enameled in white (figs. 2 and 3 *C*). The shelf and its attachments are planned so that it cannot

be easily upset by striking against it from below, while it is at the same time detachable. The L-shaped piece, the horizontal part of which fits into the groove in the table margin, and the ½ inch (1.27 cm.) rods that support the outer edge of the shelf should be of brass.

The ½ inch (1.27 cm.) square strip attached to the under-surface of the shelf to serve as a stop is of wood and extends throughout the whole width of the shelf.

Cost of marble top (1930) (Bought of Hilgartner Marble Company, Baltimore)	$230.00
Cost of monel metal sink (Bought of Lawrence Ellerbrock Company, Baltimore)	62.00
Cost of cast-iron pipe frame support and necessary plumbing (Made in University's own shop)	37.22
Casters	16.00
Total cost	$345.22

TRANSLUCENT PROJECTION SCREENS

WILEY D. FORBUS, M.D., DURHAM, N. C.

Any one who has listened to the multitude of just complaints from colleagues about the unsatisfactory demonstration of microscopic sections and lantern slides, to say nothing of the totally inadequate methods of demonstration of gross pathologic material, and who himself is conscious of the impossibility of satisfactorily demonstrating fine microscopic or gross details in pathologic conferences is conscience-stricken to the point of attempting to do something about it. Like others before me I have tried to solve this problem.

Realizing that one of the great difficulties, if not the greatest, is that large groups of people cannot get close enough to the projection screen to see details of microscopic projection, I have attempted to solve this problem by placing the screen in the midst of the group. Such an arrangement necessitates, of course, a very compact seating arrangement the limit of which is quickly reached. In order to overcome this, the obvious next step was to devise a plan by means of which both sides of the screen might be useful, thus doubling the number of people who might be seated in close range of the screen.

In order to accomplish the desired end, a number of materials possessing varying degrees of translucency were selected. By experiment it was found that an ordinary linen bed sheet, unlaundered, when stretched so that wrinkles disappear, possesses sufficient translucency to permit a very satisfactory image of a projected microscopic or

From the Department of Pathology, Duke University School of Medicine.

lantern slide field to be seen from the rear as well as from the front side. The woven structure of the material interferes in no way with the image, and the illumination of the back side is adequate to reveal the minutest microscopic detail. However, the source of illumination must be the arc-light. In my experience it is not profitable to attempt any microprojection without arc-light illumination. For ordinary lantern slides, either photographic or microscopic section slides, carbon filament lamps are quite satisfactory. The image is excellent on both sides of the screen.

A frame 6 feet (72 cm.) square was made from galvanized iron pipe three-fourths inch (1.81 cm.) in diameter. A piece of sheeting of the quality mentioned was selected and a square cut 6 inches (15.24 cm.) short of the frame in each dimension. Allowance was made for a 2 inch (5 cm.) hem along all four sides. This hem was securely stitched. At intervals of 1 inch (2.5 cm.) all along the

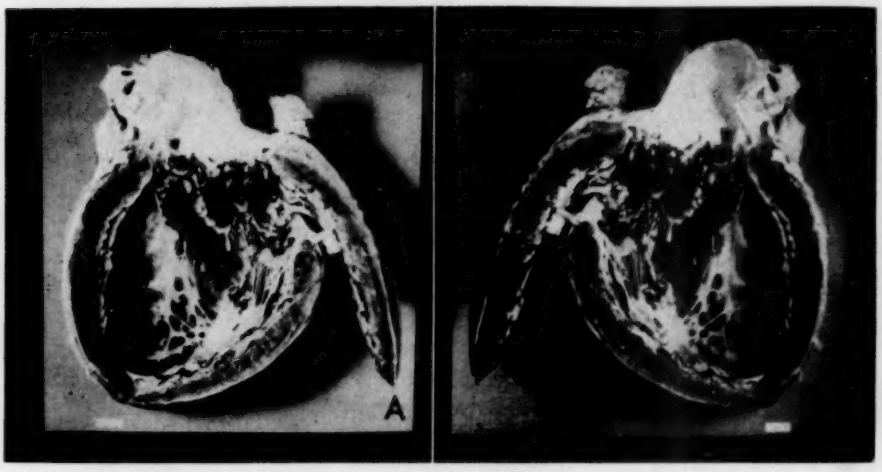

Fig. 1.—Photographs of a lantern slide projected on the translucent screen: *A*, that made from the side of the screen occupied by the projector; *B*, that made from the rear of the screen. The distance from the camera to the screen was 20 feet (6.09 meters); the time of exposure, one minute; the camera lens, Zeiss 1124404, Tessar 1:4.5, F-18 cm.; the aperture, 16; the film, par-speed; the printing time, five seconds; the developing time (print), from one to one and one-quarter minutes; the printing paper, Azo 3; the projector, Bausch and Lomb 113794, of from 110 to 125 volts, 500 watts.

four sides, round holes were punched and brass eyelets stamped in. The screen was then suspended in the frame by a continuous running cotton cord passing through the eyelets and around the iron pipe. By proper adjustment of tension it was possible to secure a perfectly flat, unwrinkled surface.

In order to eliminate the disadavantage of too great a distance between the observers and the screen, the translucent screen was suspended from the ceiling by hooks and eyes fastened to one side, the opposite side being left free. When the screen is not in use a counter weight is hooked to the free side and the screen thus

drawn up to the ceiling, leaving the room free for other purposes. The seating arrangement was so planned that the screen could be located in the midst of the group.

This technic of demonstration has been used for large clinical-pathologic conferences with great comfort and satisfaction even when the most delicate micro-projection was necessary, and when there were as many as 150 in attendance. This technic also has the added advantage of making possible the use of the autopsy room for conferences.

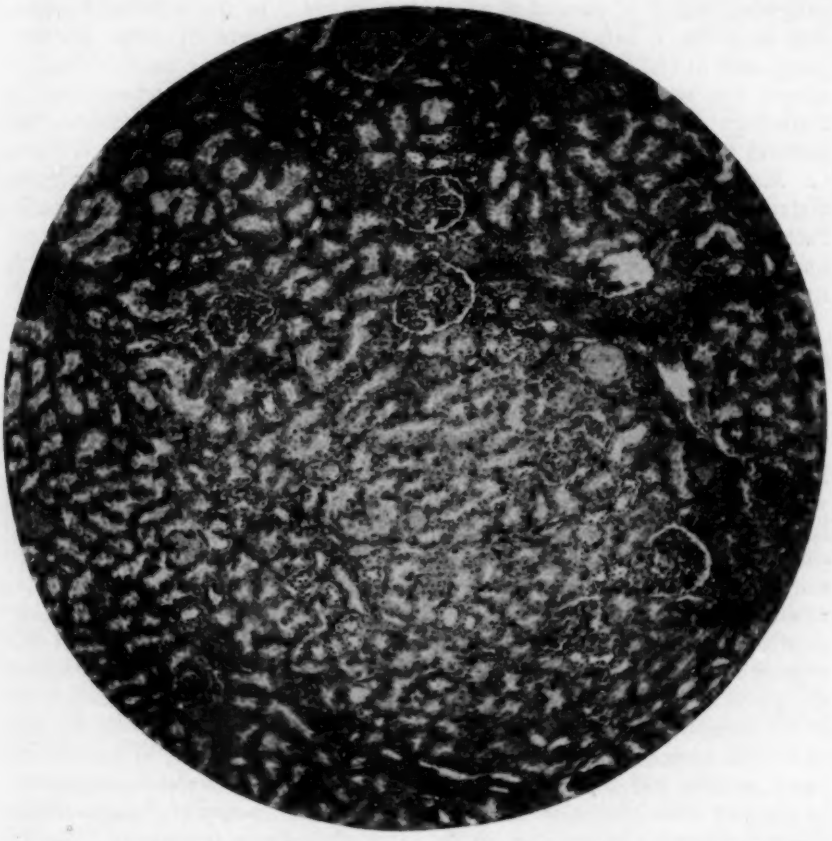

Fig. 2.—Photomicrograph of a section of kidney projected on the translucent screen constructed of sulphite paper and glass. The photograph was made from the back side of the screen. Photographs made from the front of the screen under identical conditions prove to be slightly overexposed, indicating a minor loss of illumination when the image is viewed from behind the screen. The camera lens used was Zeiss 1124404, Tessar 1:4.5, F-18, the aperture, 16; the plate, Wratten M (panchromatic); the filter, Wratten G; the exposure, forty-five seconds; the developing time, two minutes; the printing time, fifteen seconds; the paper, Azo 1; the microprojector, Bausch and Lomb 1891, with a 4.5 amperes mechanical feed arc lamp; the distance between the camera and the screen, 4 feet (122 cm.).

The efficiency of the translucent screen may be judged by comparison of the photographs shown in figure 1 *A* and *B*, which were made from before and behind the screen, all other factors in the making of the photographs of the images being kept constant in both the originals and the reproductions by the printer.

For small staff conferences of not more than from 15 to 20 people and for microscopic demonstrations, especially for small groups of students, a translucent screen of another type is necessary, since the weave of the cloth interferes somewhat with microscopic detail when the projected image is viewed at very close range. In the attempt to solve this problem I originally employed a simple piece of clear window glass, one surface of which was covered by flat white paint. Such a screen has been in use for a number of years in the Department of Pathology of the Johns Hopkins University School of Medicine, the method having been introduced, as far as I am aware, by Dr. William G. MacCallum. The difficulties experienced in obtaining a uniform distribution of the paint, which makes the chances of obtaining satisfactory and uniform illumination uncertain, suggested that a different material might be used to better advantage for covering the glass. A screen constructed in the following manner is highly satisfactory.

A square of clear window glass is first cleansed thoroughly to free the surface from all oily film and foreign particles. One surface of the glass is then covered with a relatively thick film of gum acacia dissolved in water. The solution should be quite concentrated and of a mucinous consistency. A sheet of sulphite paper (19½ pounds [8.8 Kg.] per ream) without watermark, obtainable from almost any printing shop, is first rolled loosely to avoid wrinkling and allowed to soak in water until the fiber is thoroughly wet. This roll is then placed on the gummed surface of the glass plate and unrolled. All wrinkles and creases should be worked out with the hands, leaving the paper surface flat. The paper is further flattened and the excess gum pressed out by rolling the surface with an ordinary heavy rubber double-roller such as is used in mounting photographs. Care must be exercised to prevent the separation of the fibers of the paper, since the sheet has been reduced almost to pulp by the soaking. The screen thus prepared is allowed to dry slowly and thoroughly at room temperature. Should there be some detachment at the margins of the screen, the paper can be refixed by first soaking the loose paper and applying a new film of gum. Once fixed and dried in position, the paper covering will not become detached. One should be careful to prevent any of the gum from coming in contact with the exposed surface of the paper, since this will produce a yellow stain on the paper when drying is complete.

A screen thus made may be mounted permanently in a wood frame stand. Microscopic sections can be projected on this screen at sufficiently short distances to make the finest detail of the cells clearly visible from both sides of the screen. The carbon arc must, of course, be used for illumination. A working distance between the projector and the screen of approximately 5 feet (152.4 cm.) will afford excellent projection of detail and at the same time make possible a viewing at close range by observers on both sides of the screen. The paper side of the screen should face the projector to prevent annoying reflection of the light. There will, of course, be no reflection to disturb the observers viewing the image from

the rear of the screen. The effectiveness of the screen for observation from behind is illustrated by figure 2, a photograph of a microscopic section projected on the front of the screen and photographed from behind.

These two types of screens which have been found satisfactory for every purpose have the two great advantages of permanency and cheapness. There are doubtless many materials that would serve as well as those that have been used. The selections described were made after experimental comparisons of numerous varieties of paper and cloth.

ROMANOWSKY STAINING OF TISSUES WITH BUFFERED SOLUTIONS

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AND
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Romanowsky staining of tissue sections has been generally unsatisfactory for routine use on account of the necessity of individual regressive differentiation of each section with alcohol, colophonium alcohol or dilute acetic acid to the desired point. It is often necessary to control this differentiation under the microscope.

Late in 1931 we had the fortunate experience of having a batch of sections stained by the MacNeall-French tetrachrome Giemsa modification come through beautifully stained without requiring differentiation. This accident was found to be due to an unusually acid sample of distilled water. This experience led us to try the effect of various buffer mixtures on stains of the eosin-polychrome methylene blue class, and the following procedure has been evolved.

Paraffin sections of formaldehyde-fixed or Orth-fixed material are brought into distilled water in the usual way and treated for two hours in a stain prepared as follows:

Eosinate of polychrome methylene blue[1] prepared by the Balch silver oxide method and dissolved, 1 Gm. in 25 cc. anhydrous glycerin and 75 cc. chemically pure methyl alcohol..... 2 cc.

Phosphate buffer of p_H 5.3 ($M/15$ Na_2HPO_4, 26 cc.; M NaH_2PO_4, 65 cc.; distilled water, 909 cc.)..... 50 cc.

From the National Institute of Health.

1. Ten grams of eosin water-soluble; 9 Gm. methylene blue, U. S. P. Medicinal, 88 per cent dye content.

They are then rinsed in distilled water, dehydrated with acetone (U. S. P.), cleared in xylene, mounted in liquid petrolatum (heavy, U. S. P.) and sealed with a pyroxylin cement.

Staining for shorter periods than two hours with the same or more concentrated or heated solutions has not given as satisfactory differential staining. Staining over night in a solution containing 1 cc. of stock stain to 50 cc. of buffer is very satisfactory and possibly slightly more differential than the two hour period, but the greater time requirement is an objection.

When it is especially desired to bring out such tissue elements as red corpuscles and eosinophil leukocytes, a buffer of p_H 4.8 may be employed, but nuclear staining is not as satisfactory as at p_H 5.3. On the other hand, a buffer of p_H 5.6 stains nuclei and bacteria more deeply, but suppresses eosinophils and red corpuscles. Mast cells are satisfactorily demonstrated at from p_H 5.3 to 4.8 and are more conspicuous at the more acid level. Mucin is better shown with less acid buffers.

With a p_H 5.3 phosphate buffer, red corpuscles are orange-red; eosinophil granules, red; nuclei and tigroid granules, blue; muscle and connective tissue, pink; glia and nerve fibrils, faint pink; pancreatic secretion granules, red; liver cell cytoplasm, light blue; necrotic cells, pink, and bacteria and ricketssiae, blue. The method has proved particularly satisfactory for the study of tissues of the central nervous system.

General Review

THE SCIENTIFIC BASIS OF BIOPSY IN TUMORS

C. ALEXANDER HELLWIG, M.D.
WICHITA, KAN.

CONTENTS

I. Cytologic and Histologic Criteria of Malignancy
II. Precancerous Lesions
III. Histology and Prognosis of Malignant Tumors
IV. Histology and Radiosensitivity of Malignant Tumors

I. CYTOLOGIC AND HISTOLOGIC CRITERIA OF MALIGNANCY

The microscopic diagnosis of malignancy does not seem to rest on a broad scientific foundation if Reimann's statement is true that pathologic interpretation of tissue is composed of about 90 per cent art and 10 per cent science. Fischer-Wasels emphasized that empiricism plays the principal rôle in diagnosis by biopsy.

Virchow's view that it is impossible to recognize a tumor cell under the microscope still holds today, in spite of the perfection of optical lenses and staining methods (Dietrich, Borst, Lubarsch, Sternberg, Maresch, Hertzler). By some investigators, nuclear behavior, size and number of nucleoli, loss of chromosomes, unequal nuclear division, hypertrophy of chromatin and changes of the microcentrum, of the Golgi apparatus and of Altmann's granules are thought to present criteria by which one may recognize malignant cells, but most students of the cancer problem agree that all these structures do not hold a universal key for the practical diagnosis of tumors (Da Fano, Leidenius, Horning and Richardson, Evans and Swezy, Heiberg and Kemp). Only Lipschütz believed recently that he had demonstrated a well characterized architecture of the malignant cell. By using Giemsa stain, he found in animal and human cancer cells a basophil paranuclear mass and a distinct archoplasm, which he called plastin reaction, and which he regarded as specific for blastoma. His observations were confirmed by Hirschfeld and Klee-Rawidowicz in rat sarcoma, but these structures occurred, at least in animal tumors and tissue cultures, in only a small proportion of the cells.

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The cultivation of tumor cells in vitro has not yet given as important results from the morphologic point of view as might have been anticipated. Castrén described variations in the size and shape of cultivated tumor cells, in the chromatin content of the nucleus, in the dimensions of the nucleoli, in the cytoplasmic structure and in the position of the centrosomes that were not present in resting cells, but Hirschfeld and Klee-Rawidowicz were unable to find any specific differences in morphology between normal rat tissue and rat sarcoma when observed in vitro. They observed, however, distinct differences in the karyokinesis of the tumor cells as compared with normal cells. In the tumor cells there were subdiploid to tetraploid and polyploid chromosomes, incomplete equatorial plates and pluripolar, asymmetric spindles. Their observations are not in accord with those of Goldschmidt and A. Fischer, who saw only two instances of tripolar cell division among hundreds of mitoses in tissue cultures of mouse carcinoma; the number of chromosomes in their cancer cells appeared to be as a rule reduced, but normal counts were not infrequent, and in some very large tumor cells their number was doubled. Comparing the percentage of mitoses in cultures of normal fibroblasts and carcinomatous tissue, A. Fischer and Parker found the incidence of dividing cells in malignant tissue to exceed greatly that in normal tissue, in spite of the fact that the rate of growth of normal tissue may exceed in vitro that of carcinomatous tissue by 700 per cent.

According to M. R. Lewis and Lockwood, the fibroblasts of the Walker rat sarcoma contain twice the normal number of chromosomes, but the cells of mammalian carcinoma thus far cultivated apparently show no specific morphologic characteristics that would differentiate them from normal epithelium.

A. Fischer's physiologic studies on tumor cultures have thrown much light on the nature of malignant cells, but are at present only of theoretical interest. He reported in 1928 the following phenomena that he thought were characteristic for the malignant cells: (1) Under culture conditions, optimal for normal tissue, mouse carcinoma grows much more slowly than normal tissue; (2) carcinoma cells continue to proliferate in pure serum, while normal cells do not; (3) carcinoma cells grow well also in inactivated embryonal tissue extract, which is unsuitable for normal cells and, (4) carcinoma cells overgrow all kinds of homologous tissue cells. But his conclusions in the latest edition of his book on tissue culture (1930) were less optimistic, and also he had to admit that this modern method does not reveal specific, but only quantitative, differences in growth between the normal and the malignant cell.

The metabolic investigations of Warburg and his co-workers hold at present the foremost interest in the field of cancer research, but have

failed so far to lead to any practical results. In Warburg's own opinion, they confirm the standpoint of the histologists that there are no principal, but only gradual, differences between benign and malignant tumors. Attempts to diagnose human tumors on the basis of Warburg's observations have met with failure (Lauros).

Roffo's claims that the determination of the hydrogen ion concentration in tissue cultures permits, or excludes, a diagnosis of cancer were refuted by Bottin.

Human cancer cells apparently are not as well adapted to cultivation as those of animal tumors. The few workers who have undertaken this difficult task (Kikuchi, Castrén, Lemmel and Löwenstädt) have obtained only very scanty emigration of single cells in vitro, the nature of which was not even always fully established. Lauche reported that his culture of cancer of the human breast was the oldest one on record, since it showed mitotic figures in tumor cells three weeks after explantation. His observation in a mixed culture of human cancer and embryonal heart tissue, where the normal heart cells had overgrown the tumor tissue, makes one extremely cautious in drawing definite conclusions on human pathologic changes from the present results of tissue culture. Kredel seems to be the only one to assert that the method of tissue culture is a practical means for studying the cellular components of human tumors, at least of tumors of the brain. He obtained in 62 per cent of 37 tumors of the brain a satisfactory growth in vitro and observed a characteristic appearance and behavior of the outwandering cells for each type of tumor. Much less successful were cultures of human meningiomas in the hands of Buckley and Eisenhardt; in but 1 of 22 tumors was an outgrowth of cells obtained that could be considered as tumor tissue.

The study of experimental cancer has also failed to establish reliable cytologic criteria of malignancy. Yamagiwa and Itchikawa, who were the first to succeed in producing tar carcinoma in rabbits, pointed even then to the difficulty of distinguishing very young tar carcinoma from benign folliculo-epithelioma. As a feature representing the initial step in malignant transformation, they recognized that some or all of the epithelial cells assume a fainter stain with hematoxylin than does normal epithelium or benign papilloma. Fukuda stained sections of early tar cancer with Bielschowsky's method. Whereas in normal epithelium only the deeper site of the basal cells is clear, in tar carcinoma the interpapillary epithelial processes became clearer with the progress of epithelial growth, until finally whole cell layers failed to take up the silver stain.

Deelman and van Erp, studying the epidermoid changes due to application of tar in mice, arrived at the conclusion that cytologic criteria do not at present permit a differentiation between regenerating,

precancerous and cancer cells. Also Jaffé and Eliassow emphasized that microscopic methods fail completely in diagnosing the beginning stage of experimental tar cancer. Of their 9 rabbits in which histologic examination of excised tissue from a new growth revealed definite cancer, only 4 developed a progressive malignant tumor, while in 5 the lesion proved to be harmless.

Schuster examined skin lesions of white mice after different periods of application of tar for the purpose of studying the arrangement of chromosomes in the development of carcinoma. There were typical mitoses in the hyperplastic, papillomatous and precancerous stages, while in developed tar carcinoma he found only slightly atypical figures in the well differentiated carcinoma cells and marked atypical arrangement of the chromosomes in the immature tumor cells. He concluded that the origin of cancer is not due to a primary change in the chromosome constitution—as Boveri and von Hansemann hypothecated—but that irregular mitoses are secondary changes, due to excessive cell proliferation.

A reliable cytologic diagnosis of cancer would be of the utmost practical importance in the examination of pleural and ascitic fluid. The most thorough investigation of this particular field was undertaken by Quensel, comparing his findings in pleural and ascitic fluids with anatomic observations at operation and autopsy. He employed supravital staining of moist preparations with methylene blue (methylthionine chloride, U. S. P.)-cadmium and sudan-cadmium, and stated that he was able to recognize malignant cells in most of his carcinomatous exudates. Quensel, however, pointed out that there is no general cytologic formula that can be applied in all cases, because the number and form of the tumor cells vary greatly. The cytologic picture depends on the nature of the primary tumor and on that of the malignant process in the serous cavity. In scirrhous carcinoma, the number of tumor cells in the exudate is small, or the cells may be absent altogether, while in medullary cancer a larger number of cells is usually found. In carcinomatous exudate, the malignant cells may occur singly or in groups. Endothelial cells are found more commonly in thin sheets, while tumor cells are arranged in different levels. The tumor cells are frequently larger and often stain more deeply than the endothelial cells, and their nuclei are often unusually large. As a most important characteristic of malignant cells, Quensel found large size, increased number and irregular form of the nucleoli.

Henke and Dietrich doubted, in spite of Quensel's valuable contributions, whether a reliable diagnosis can be made from single cells in body fluids, urine, stomach contents or feces except when small fragments of tissue are obtained.

Foord, Youngberg and Wetmore found in all serous fluids from carcinoma of the serous cavities masses of large cells, irregular in size and shape, often vacuolated and sometimes with mitotic figures. The presence of these cells in the exudate was regarded by these authors as highly suggestive of a malignant condition, but they held that a definite diagnosis is more safely made on the embedded sediment, in which fragments of tumor tissue can often be found. Confusion results in examination of smears when degenerated forms of large nucleated cells, either serosal desquamations or cells of the macrophage type, are seen. Arnstein and Huppert reported cytologic observations in 115 pleural effusions. They pointed out that effusions from various sources—hydrothorax, tumors and inflammatory conditions—cannot be safely differentiated by morphologic examination. According to Koeniger, Stadelmann and O. Fraenkel, peculiar cells of signet ring shape are so frequently present in pleural and peritoneal exudates of cancers as to be characteristic of cancer. But Henke and Andres denied their diagnostic significance, since they found these cells in cases that proved not malignant at necropsy and, on the other hand, they were absent in cases of certain malignancy.

Few authors today rely on the cytologic diagnosis in examining surgical specimens. The rapid method of Dudgeon and Patrick consists in scraping off cell smears from the cut surface of the doubtful tumor with a sharp knife, fixing the smear for from two to ten minutes in Schaudinn's fluid and, after washing in alcohol and distilled water, staining the slide with hemalum and eosin. This method failed in only 9 of their 200 cases. The variation in the nuclear size is utilized by Dengler as a criterion of malignancy. A rice seed-sized piece of tissue removed from the suspicious part of the biopsy specimen is dissected with the help of two needles in physiologic solution of sodium chloride. After addition of a drop of 1 per cent acetic acid, this preparation is examined with high magnification, and the nuclei of the tumor cells are counted according to their size. The smallest nuclei present are designated as 1, the nuclei twice the size as 2, and so on up to 7. The result is expressed as the quotient of the number of different sizes counted divided by the total number of nuclei counted. If 50 nuclei are counted, the quotient for carcinoma is always above 0.1; usually it is 0.14. Dengler applied his method successfully in 100 fresh operative specimens.

Babes recommended that in suspected cancer of the uterine cervix cell smears be examined in place of diagnostic specimens, the excision of which, he regarded as too dangerous. The suspicious lesion is wiped with gauze, and the material is taken with a platinum loop, fixed with alcohol and stained on the slide. A diagnosis of carcinoma is made from the atypical character of the epithelial cells. In the hands of Babes, this method gave 18 positive results in 20 cases that proved to be carcino-

matous at operation. Viana, employing the same technic, confirmed, by paraffin sections, the diagnosis from the smears in all of his cases of carcinoma.

In Schiller's opinion, cell smears alone are not sufficient for a reliable diagnosis of cervical carcinoma. But by removing the squamous epithelium in its entirety from the substratum, he was able to diagnose correctly 242 lesions of the cervix uteri. After the cervix has been painted with compound solution of iodine, normal epithelium becomes dark brown within a few seconds, while a pathologic surface stays unstained. Iodine negativity attracts attention to suspicious areas in which the epithelium is pathologically changed, but not necessarily carcinomatous. The nature of the pathologic process can be determined by histologic examination of the curetted epithelium. In sections, carcinoma is diagnosed, according to Schiller, from the characteristic atypical and polymorphous appearance of the cells. Deeply penetrating growth clinches the diagnosis, and can be shown by serial sections, but is not absolutely necessary to establish the diagnosis of carcinoma. Additional histologic characteristics of malignancy are sudden sharp transition of normal epithelium into carcinoma, disappearance of glycogen in the section stained by the method of Best and a sudden increase of oxygenophilia with the potassium permanganate stain of Unna. According to R. Meyer, the glycogen reaction is unreliable for the diagnosis of malignancy and according to Frankl the whole method of Schiller is still in the experimental stage.

While these cytologic methods relied more or less on the arrangement and the polymorphous character of many tumor cells in a given case, MacCarty claimed that he could make the diagnosis of malignancy from a single cell, and that in his experience the "single cell diagnosis" had never failed. According to him, there is no specific staining reaction for the cancer cell, but there are certain physical criteria by which it may be recognized in most, if not all, instances. MacCarty found the mitoses in malignant cells sometimes multipolar, but never asymmetric or irregular. The nucleolar-nuclear ratio in cancer cells is approximately 1 : 23, while in regenerative cells it is 1 : 50 or more. The regenerative cell is more delicately constructed, and its nuclear granules are usually finer. Malignant cells actually exist, according to MacCarty's belief, before the invasion of tissue—for instance, within milk ducts of the mammary gland—and they are microscopically indistinguishable from cells in lesions which all pathologists call cancer. Still MacCarty did not call these cells carcinomatous when inside of milk ducts, and he did not advise, in these cases, a radical operation, since none of his patients in whom these atypical cells had been found had died of cancer. With this conception, the "malignant cell" of MacCarty loses all practical significance. I am unable to detect anything in MacCarty's description

which has not been known since Lebert's and Hannover's unfortunate attempts in the middle of the last century to characterize morphologically the "specific cancer cell." Neither in his numerous papers on this subject, nor by his drawings and photomicrographs, did MacCarty explain how his single cell diagnosis is achieved, and he did not advance evidence in support of his assertion that the specific cancer cell is the key to diagnosis and prognosis.

Only in the special field of tumors of the brain does the cytologic diagnosis seem to be feasible. Eisenhardt and Cushing adopted the supravital technic as the most favored routine method of diagnosing tumors of the central nervous system, this being of particular value in the cytologic differentiation of the various types of glioma. A minute portion of the fresh specimen is separated with dissecting instruments and placed on a glass slide. A drop of aqueous solution of neutral red (1: 10,000) is added directly to the tissue and a cover glass placed over the tissue, which is carefully spread by gentle pressure on the cover glass. This method offers an opportunity for the study of cells that have not undergone shrinkage and distortion as a result of fixation and cutting, but that are seen in their entirety while they are still living. Under oil immersion, single cells, such as astrocytes and oligodendroglia, may be beautifully defined with all their delicate processes, which are rarely seen intact in fixed histologic sections.

The finer study of cell characteristics is of great importance in the diagnosis of carcinoma of the cervix according to R. Meyer. He admitted that Schiller's new method of scraping off the surface of suspicious lesions of the cervix may often furnish sufficient material on which to arrive at a positive diagnosis, but held that it did not in every case. It will fail sometimes because cancer cells may be well differentiated and of almost typical structure, while in healing erosions immature cells of very suspicious appearance may be found. Lack of differentiation of the epithelial cells, as compared with the normal prototype, and such nuclear abnormalities as greater size and hyperchromatosis form the basis for differentiation of very early cancer and inflammatory conditions, but these cell changes must be found in all epithelial layers and over a large area of the tissue to be of decisive value. Mitoses and especially irregular forms are often missed in young stages of carcinoma. On the other hand, mitotic figures seem, in Novak's opinion, to be suggestive of malignancy. He stated that he had almost never seen them in the basal layer under benign conditions and did not recall ever having found them in the superficial layers except in malignant conditions.

The cytologic changes that are so valuable in the diagnosis of early cancer of the cervix are much less helpful in cancer of the uterine body. Benign hyperplasia may reveal thickly crowded glands in some of which

the epithelium may be in several layers with dark-staining nuclei. Mitoses may be numerous. Structures like these have more than once been wrongly diagnosed as malignant adenoma (Novak). In advanced stages of adenocarcinoma, the glandular architecture is so characteristic that a few glands in curetted material will permit a positive diagnosis (Schottländer). The carcinomatous glands are not only much longer and wider, but often labyrinthine owing to irregular papillations and complicated branching. Multiple cell layers are usually found, at least in some glands. The stroma between the glands is almost completely missing. But these changes are to be considered as evidence of malignancy only if encountered in the endometrium itself. In polypi of the uterine body, marked proliferation and irregular branching of the closely packed glands and stratification of their epithelial lining have to be regarded as benign changes as long as they are restricted to the polyps. Hintze observed 17 cases of these polyps in a twenty year period, and in none of them was malignancy observed later.

In the microscopic diagnosis of early cancer of the skin, the most valuable single factor is the assumption of younger, more vegetative qualities on the part of the hyperplastic cells involved (White and Weidman). The cytoplasm of the cancer cells has a rounded off contour; its substance is more hyaloid than normal and is different in tint from the normal.

In tumors of the bladder, also, the microscopic diagnosis rests often on atypical cell changes. In Aschner's material, 30 of 138 papillary carcinomas did not show in the biopsy specimens any evidence of invasion of the pedicle. The cytologic changes that branded these tumors as malignant were either slight and limited to a small part of the growth or marked and present throughout the papilloma. The changes on which Aschner based his diagnosis of malignancy were the presence of large cells with irregular, deeply staining nuclei, cells with atypical mitoses, pyknotic nuclei or lobulated forms, intensification of cell membranes with a tendency toward the squamous cell type, loss of palisade arrangement and loss of uniformity. Ewing stated that for a long time he had noted that the presence of a few atypical cells in a papilloma of the larynx generally signifies that the disease will recur and will kill the patient sooner or later; and that in tumors of the bladder the presence of small groups of atypical cells in an otherwise benign papilloma carries with it an increased gravity in prognosis.

In 1908, Lubarsch stated that in principle it is permitted to diagnosticate cancer only when one has found sure and clear criteria of destructive growth. Orth, Cornil, Borst and others regarded as the most important criterion of glandular carcinoma the perforation of the basement membrane. There is general agreement that invasion of tumor cells into the surrounding tissue and destruction of the host organ are

conclusive evidence of malignancy, even when cytologic criteria of malignancy are absent. Basing his judgment on 108 cases of malignant goiter, Graham arrived at the conclusion that it cannot be decided by cytologic characteristics whether an adenoma of the thyroid gland is benign or malignant. The only morphologic evidence of malignancy in tumors of the thyroid gland is the invasion of blood vessels.

Aschner found among his large number of tumors of the bladder a small group of infiltrating carcinomas that were characterized by a cell growth indistinguishable from that of benign papilloma. Yet the tumor invaded the pedicle, infiltrated the wall of the bladder and its vessels and eventually produced distant metastases. In these rare instances, the diagnosis could not be made, unless tissue had been removed from the infiltrated base.

Since Virchow reported several cases of metastasizing enchondromas, it is known that almost any histoid, microscopically benign tumor—myoma, lipoma, hemangioma—can produce distant metastases. R. Meyer described a sarcoma of the endometrium of typical cell structure, the malignant character of which could be recognized only from the destruction of uterine glands.

There are, on the other hand, processes with undoubted heterotopic growth, which are entirely harmless; for instance, adenomyoma of the uterus and other organs. In Ewing's and R. Meyer's treatises, there are photomicrographs of a minute benign myofibroid invading the lumen of a uterine vein. In erosion of the cervix, there may be a marked dipping in of squamous epithelium independent of the glands. The histologic changes in highly epidermoid polypi of the cervix may also be easily mistaken for cancer, especially if squamous epithelial cells have advanced deeply into the glands and have replaced the cylindric lining. The misinterpretation of this entirely benign intermingling of squamous and cylindric epithelium in cervical erosions and polyps still leads to hundreds of unnecessary hysterectomies (R. Meyer).

A common error in the diagnosis of urethral caruncle in the female results, according to Ewing, from the deep normal invaginations of the epithelial lining of this structure. On section, these invaginations may appear as displaced islands of atypical epithelium, strongly resembling epithelioma. Only the uniformity as regards size and appearance of the epithelial cells, and the fact that for the most part they are properly oriented, dispose of the suspicion of malignancy.

The human epidermis has the capacity to regenerate to such a degree as to simulate cancer morphologically (White and Weidman). In the presence of cutaneous defects known to be chronic the significance of carcinoma-like hyperplasias should be heavily discounted. Deep permeation, below the level of the sweat glands, is the only certain histologic criterion in some cases. Sweat duct epithelium readily becomes

hyperplastic in connection with suppurative and irritative processes and may be sufficiently irregular to suggest carcinomatous changes. According to Frei, the so-called carcinoma-like condyloma acuminatum of the penis is not seldom mistaken for true cancer from the microscopic structure, especially in the presence of horny pearls.

Heterotopic growth is known to be especially confusing in biopsies of laryngeal lesions. Paltauf never diagnosed a section from the larynx without knowing the clinical history of the case. He stated that after treatment with caustics the epithelium may invade irregularly the deeper structures. Especially in tuberculosis of the vocal cords, the epithelium frequently invades the underlying tissue and may even penetrate into the cartilage (Manasse). Hajek collected several cases from the literature, in which experienced pathologists had diagnosed carcinoma from biopsies, but in which the removed larynx showed only tuberculous inflammation.

Invasive epithelial growth is therefore not always identical with carcinoma, and—on the other hand—in biopsies of very early cancer destructive and heterotopic properties may be missed.

II. PRECANCEROUS LESIONS

No morphologic method can decide whether a noncarcinomatous atypical cell proliferation will actually develop into cancer or prove to be entirely harmless. The deciding factor when such a lesion results in a malignant tumor is apparently an individual predisposition the nature of which is completely unknown. By inoculating a saturated solution of scharlach red in the rabbit's ear, Fischer-Wasels produced atypical epidermoid growth, which completely resembled that preceding cancer, but which never attained malignant character unless the animal received the smallest doses of arsenic. The study of experimental cancer has not offered any histologic criteria for deciding whether a precancerous tar papilloma will be followed by autonomous malignant growth or remain self-limited.

Ewing's contention that in a given case one may be dealing with a condition in the process of becoming cancer may be theoretically true, but cannot be proved with present methods. The confusion is increased by using interchangeably the terms "precancer" and "beginning carcinoma." Radical pathologists like Schauenstein, Schottländer and Rubin classify as beginning cancer the same atypical tissue changes which, lacking absolute histologic criteria of early malignancy, may prove to be harmless epithelial proliferations. The terms "precancerous lesion" or "potential malignancy" have been too often used as a basis for unnecessary radical operation. There is no reason why such a case cannot be watched by a competent observer for a few weeks, when

a new exploratory excision can be made, or until more definite though still early signs develop (Frank). A long-continued follow-up by Pemberton and Smith of patients whose cervical specimens were microscopically suspicious failed to reveal a later development of carcinoma in any instance. Ewing's writings indicate that he favors the theoretical conception of a precarcinomatous stage of epithelial proliferation passing by insensible gradations from normal cells to fully developed cancer, but that in practice he regards changes without definite signs of malignancy as benign and does not permit including "precancerous lesions" in the statistics of cured cancer.

As chronic endocervicitis and laceration of the cervix, as well as hyperplasia of the endometrium and submucous myofibroids, are commonly found present with or preceding cancer, these conditions are often classed without sharp critique as precancerous etiologic factors (Villard and Montel, Ter-Gabrielian, Bailey, Lahm, Hofbauer). No statistics taking into consideration the percentage of these changes in cancerous and noncancerous women have ever been compiled, and it would seem that the frequency of these benign conditions alone disproves the theory of an etiologic relationship with cancer.

Leukoplakia of the female organs was described first by von Franqué as a precursor of carcinoma. Hinselmann regarded it in the cervix not merely as a precancerous condition, but as an early noninvasive stage of carcinoma. Both views were rejected by R. Meyer, who had often seen multiplicity of cell layers, with elongation of rete pegs and papillary overgrowth of spinous cells, sometimes with hornification, in cases that by the clinical course proved to be benign. In their study of 21 cases of vulvar carcinoma, Graves and Smith found leukoplakia 16 times and kraurosis 14 times, and they feel that there is a close relationship between these two processes and cancer. Of Taussig's 29 cases of vulvar carcinoma, 60 per cent showed the malignant changes taking place in an early hyperplastic area, and 40 per cent, in a late atrophic area. In Taussig's opinion, squamous cell carcinoma of the vulva springs from leukoplakic vulvitis in almost every instance, and the latter undergoes malignant change eventually in at least one half of the cases. Rentschler, on the other hand, in a review of 71 cases of primary vulvar carcinoma, found that in 40 per cent the patient gave a definite history of preexisting pruritus, but that only in five cases was leukoplakia coexistent with carcinoma.

Kutzmann observed 67 cases of leukoplakia of the renal pelvis, 11.9 per cent of which were combined with carcinoma. Among 3 cases of leukoplakia of the urinary bladder, von Borza saw 2 in which this organ was also affected with squamous cell carcinoma. Kretschmer believed that leukoplakia of the urinary organs is probably much more common than it is generally thought. In only 1 of his 13 cases was carcinoma

associated with leukoplakia of the bladder. By collecting from the literature the cases of leukoplakia and carcinoma of the urinary organs, Patch hoped to answer the question whether leukoplakia and cancer are as intimately related to each other as is generally accepted. Of the reported 121 cases of leukoplakia and 152 cases of squamous cell carcinoma of the urinary tract, only 13 showed coexistence of both processes.

According to Brüning, leukoplakia of the buccal mucosa is often followed by carcinoma. No unanimity of opinion, however, exists in regard to the frequency of this transformation (from 10 to 53.8 per cent). Lazarus believed that one third of all cancers of the tongue arise from leukoplakic areas. Herzen and Jenckel insisted on radical excision of all leukoplakic areas in the mouth as a prophylactic measure. Also Deelman called the leukoplakia that occurs in the upper parts of the respiratory and alimentary tracts a true precarcinomatous change. He found at the periphery of the carcinoma that develops in leukoplakia the gradual transition from hyperplastic epithelium to neoplasm and the morphologic substratum of precarcinoma in its final development. Schaer, on the other hand, doubted whether leukoplakia plays as important a rôle in the genesis of cancer as many believe. He found in 237 esophagi without cancer, obtained at autopsy mostly from men above 40 years of age, 67 per cent affected with leukoplakia. In his series there were 17 traction diverticula that not seldom showed atypical proliferation of the surface epithelium, and Schaer was of the opinion that these diverticula may predispose to the development of esophageal cancer much more than leukoplakia. Sharp, however, concluded from one observation of a case in which relatively early carcinoma was coexistent with far advanced leukoplakia of the esophagus, that the irritating factors may bring about a leukoplakic response in one area, and that the same or additional factors may cause cancer in another.

Benjamins described 3 cases of laryngeal carcinoma with continuous transitions from precancerous changes to fully developed carcinoma. He concluded from these observations that every papilloma showing hyperkeratosis should be treated as a malignant tumor. Also Tucker and Jackson regarded the evidence as conclusive that cancer of the larynx develops from nonmalignant lesions.

There is wide difference of opinion regarding the possible transformation of chronic gastric ulcer into carcinoma. While Konjetzny placed the percentage at 3 and Hauser at 6, Wilson and MacCarty reported it as occurring in 71 per cent. Klein and Demuth studied ulcers and carcinomas of the stomach with the aim of determining whether any histologic changes other than those easily recognized as definite carcinoma might be considered characteristic of malignant transformation of

an ulcer. They doubted that the histologic diagnosis can be based—as Moszkowitz believed—on deeply stained epithelial cells, no matter how atypical or heterotopic they are.

Stewart believed that an important and intimate relationship exists, both in the stomach and in the large intestine, between simple adenomatous polyp and carcinoma, but the ultimate full development of a malignant condition is in most cases confined to a single focus. Hurst found in about 0.5 per cent of his cases of gastric carcinoma diffuse gastric polyposis and in 4.5 per cent simple adenoma as a precursor of malignancy. According to Miller, Eliasow and Wright, carcinomatous polyps of the stomach are more frequent than has been generally believed; both the history and the pathologic data suggest that they usually originate in polyps of a benign nature. The authors observed 8 cases of carcinomatous polyps in a series of about 200 operations for cancer of the stomach, constituting about 4 per cent of the group.

In adenoma of the stomach and of the intestines, Bloodgood advised radical resection as a prophylactic measure. According to Lockhart-Mummery, Dukes, Rankin and Bargen and many others, rectal adenomatous polyps constitute the most dangerous predisposing factor in the development of rectal adenocarcinoma. The adenomas are usually numerous and often separated from one another by normal mucosa. The bowel may remain in this condition for many years, or at any stage of the epithelial proliferations the epithelium may abruptly assume those invasive properties recognized clinically and histologically as cancer. The incidence of malignancy in multiple polyposis is generally accepted as being from 40 to 50 per cent. But according to Bargen and Rankin, it is impossible from histologic and clinical examination to predict whether or not a given polyp will become malignant. While most of the authors did not have the opportunity actually to observe a malignant transformation in a particular polyp in any case, Schmieden and Westhues described all histologic transitional stages from harmless adenomatous hypertrophy of the mucosa to polyps with partially undifferentiated cells leading up to fully developed adenocarcinoma. Westhues classified the different histologic pictures into 3 groups. His third—which alone he calls the precarcinomatous stage—is characterized by invasion of the pedicle and perforation of the muscular layer, but there arises the question whether this third stage with definite signs of malignancy should not be called carcinoma. Westhues' classification of intestinal polyps into 3 groups is accepted by Fitzgibbon and Rankin. In the tumors belonging to their third group—the definitely precancerous lesions—the cells could not be distinguished morphologically from those seen in outright cancer. For 19 of their 24 cases of cancer they found indisputable proof that the sites of origin of the malignant growths were in polyps, and they concluded that cancer of the colon develops usually

from an earlier stage as a polyp. Fitzgibbon and Rankin regarded it, however, as an impossible task to determine how many polyps actually become cancerous.

This difficult problem was attacked by Feyrter. He examined at autopsy the large intestines of 1,110 patients over 20 years of age and found in about one third of them adenomatous proliferations in the colon. The total number of polyps found was about 1,000, but only 6 of these were carcinomatous and 4 suspicious for malignancy.

Of great interest is the case reported by Hullsiek of multiple polyposis of the colon, in which the first biopsy did not show any histologic evidence of malignancy. Two years later an adenocarcinoma was revealed by biopsy at the rectosigmoid junction. The autopsy showed, besides this carcinoma—with no suggestion of its having arisen from a polyp—no carcinomatous changes in any of the polyps that extended from the rectum up to the ileocecal valve. Observations of this kind led Stahr to the conclusion that rectal polyps like other atypical epithelial proliferations are not true precancerous stages, but can be regarded only as indicators of some kind of irritation that is capable eventually of producing cancer under circumstances not yet understood.

There is bewildering dissension about the practically important question whether chronic cystic mastitis has to be regarded as a precancerous lesion. In my opinion, this problem will never be solved by present histologic methods alone, but only by long-continued clinical observation of nonradically treated cases. The morphologic appearance of atypical epithelial proliferations within ducts and acini in chronic cystic mastitis is seldom definite enough to enable a dogmatic interpretation of its biologic state. The disagreement of different pathologists in a given case of proliferant chronic cystic mastitis demonstrates well the limitations of present histologic methods. At a pathologic conference in 1931, Bloodgood invited 50 experienced pathologists to diagnose the slides of 10 lesions of the breast that were known to be clinically benign. Not in one single instance was there general agreement regarding the significance of the microscopic picture.

The fact that carcinoma of the breast is often found associated with chronic cystic mastitis is easily explained by the high incidence of the latter. Goens found at autopsy in one third of all women over 40 years of age changes typical for chronic cystic mastitis, and Hahn saw the same condition in 11 of 48 women younger than 40 years. Still higher is the incidence in the material of R. Jaffé. He observed in 100 autopsies of women over 40 years of age chronic cystic mastitis in 93 per cent. In 65 per cent, he found marked epithelial proliferations of the milk ducts that were indistinguishable from changes called precarcinomatous by many pathologists.

Cheatle believed that 20 per cent of all cancers of the breast begin with chronic cystic mastitis. The appearance of the latter disease and its subsequent course occupy the same age decades—25 to 30 years—as tar carcinoma does in man, and the carcinoma in each appears to be the result of a continuous process which as a rule takes a definite time. In early mammary carcinoma there is, according to Cheatle, an epithelial neoplasia the cells of which are still contained within their normal boundaries, and these cells resemble precisely in morphologic appearance those that have invaded the stroma. Hyperplasia of the elastica surrounding only those terminal ducts that contain epithelial cells of malignant character is regarded as a distinct indication of the dangerous state. But Cheatle also had to admit that, aside from arousing suspicion, the matter must remain a question until the biologic state of epithelial cells can be determined with greater certainty than can be elicited from their morphologic characteristics only.

Goldzieher and Kaldor examined 47 specimens of chronic cystic mastitis. In 12, they found cancer; in 4, precancerous changes. In the latter, invasive growth could not be demonstrated, yet the morphologic appearance of the hyperplastic epithelium was suggestive of malignancy. These precarcinomatous changes were identical with proliferations that were observed in the vicinity of frankly carcinomatous foci within milk ducts. The authors could not prove, however, whether or not these precancerous changes were about to develop invasive tendency, although "it seemed highly probable."

Semb made an exhaustive anatomic study of 148 cases of chronic cystic mastitis and described microscopic changes passing by insensible gradations from simple microcystic chronic mastitis into atypical hyperplasia and finally leading up to invasive carcinomatous neoplasia. He concluded that chronic cystitic mastitis is a true precancerous lesion which eventually will result in cancer and which requires removal of the whole mammary gland. Also Klose and Sebening regarded prophylactic amputation of the breast as the only logical treatment for chronic cystic mastitis. The frequency of malignant transformation after partial resection of the diseased area of the breast is in their opinion "formidable." Benda found in most specimens of chronic cystic mastitis such atypical epithelial proliferations that he felt sure that this is a precancerous condition with grave prognosis. Ewing concluded from his vast experience that chronic cystic mastitis is a very important condition predisposing to mammary cancer. From the practical standpoint of prognosis, Ewing regarded it as safe to remove the whole breast or the whole affected segment when an incision is required for diagnosis. In case of malignancy, the correct surgical procedure can be determined during exploration. The course of the established disease

is, in Ewing's opinion, generally progressive, and most cases of chronic cystic mastitis eventually terminate in carcinoma or in surgical removal of the breast.

Clinical considerations, however, suggest that chronic cystic mastitis will often not develop into cancer and show, on the other hand, that many cancers of the breast are not preceded by a precancerous stage. Of 617 women with cancers of the breast who were operated on by Läwen, only 11 had, several years before operation, chronic mastitis as proved by biopsy, and 64 had clinical symptoms of chronic mastitis many years preceding the development of cancer. Bloodgood, from the standpoint of a clinical and anatomic study of 350 cases of chronic cystic mastitis, concluded that this condition has no etiologic relationship to carcinoma, and that women with this disease are no more in danger of acquiring cancer than women of the same age without it. No matter what the operation was in his 350 cases, there was no death from carcinoma of the breast in a period of over twenty-five years. Also the so-called diffuse adenomatous variety of chronic cystic mastitis, which Bloodgood believed up to 1906 to be associated with cancer in at least 50 per cent of the cases, is, according to his recent statements, not a true precancerous lesion, its association with cancer being only incidental. In probably 70 per cent of patients with chronic cystic mastitis coming early for medical observation, operation can be decided against by palpation alone. Of the 30 per cent in whom the breast must be explored, one half or more reveal benignancy on gross inspection and examination of frozen sections. In 40 of 43 patients with chronic cystic mastitis whom I observed, only partial resection of the diseased area was done, and not one of these returned with a malignant growth. In only 3 was a radical operation advised after biopsy—this on account of intraductal proliferation so marked and so atypical that suspicion of malignancy was aroused, although no frankly invasive epithelial growth could be demonstrated. To remove all breasts with chronic cystic mastitis would, I believe, entail an unnecessary mutilation in at least 90 per cent of the cases.

Of greatest importance in evaluating properly the finding of atypical epithelial proliferation in biopsy specimens is the work of Meeker. She dissected at autopsy normal vocal cords and their attachments from persons aged from 2 months to 80 years, with no history of laryngeal lesions. In these normal specimens, great activity of the squamous epithelium with filling in of wide surface openings of the ducts and fusion into solid masses was present. Within the deeper gland ducts, papillary thickenings of the epithelium as well as a tendency to metaplasia were common. These changes were exactly like those that are called precancerous by many pathologists. Meeker's observations certainly suggest caution in basing prognostic conclusions on more or less

atypical cell proliferations—not only in the larynx, but in any other part of the body where specimens for biopsy are obtained.

In my opinion, "precancer" as a histologic diagnosis is meaningless. In diagnosing a lesion by biopsy, either the pathologist should take the full responsibility by pronouncing the lesion malignant or benign, or—if he is unable to arrive at a definite diagnosis—he should have the courage to admit that he does not know and leave the responsibility to the clinician or to a more experienced histologist. Nothing is gained by calling a suspicious change in the tissue a precancerous lesion, a term which is a confession of ignorance.

III. HISTOLOGY AND PROGNOSIS OF MALIGNANT TUMORS

From the beginning of the microscopic era, the tissue experts have formed from their histologic observations an opinion concerning the progress of the neoplastic disease. Von Hansemann regarded it as a law that tumors disseminated through the body show a high degree of anaplasia, while those of unusual local growth without dissemination show little anaplasia. Henke, Borst, Hertzler and Herly accepted this theory in a general way, but they called attention to the frequent exceptions. In 1915, Ewing regarded as insufficient a pathologic diagnosis simply of carcinoma or sarcoma, since some processes to which these terms are attached are self-limiting, while others are invariably fatal. He believed that the pathologist is able to interpret the clinical diagnosis from the microscopic section in Hodgkin's disease, malignant lymphosarcoma, osteogenic sarcoma and many other tumors of which the prognosis is practically always fatal. In another group, the potential malignancy of the tumor may be judged with much accuracy from its histologic structure, but its actual clinical course may be subject to wide variations, depending chiefly on age, location, size and duration.

Five years after Ewing's cautious conception of the relationship between histology and clinical prognosis of tumors, Broders aroused the interest of surgeons and pathologists by his statement that the clinical course of many cancers may be quite accurately predicted by analysis of the histologic structure alone, without taking clinical factors into consideration. Basing his work on von Hansemann's law that the more highly differentiated the cells, the lower is the malignancy of a tumor, he graded carcinomas of the lip and other regions into 4 grades according to the differentiation of the tumor cells, and presented statistics to prove that these histologic features govern the life expectancy in a given case. According to him, cancer of grade 1 shows practically no tendency to metastasize, and therefore in dealing with such neoplasms he considered it unnecessary to remove the regional lymph nodes. As, on the other hand, practically all cancers of grade 4 with metastases prove fatal, he advised the surgeon not to subject patients showing these cancers

to an operation involving the regional lymph nodes, unless these nodes are in close proximity to the primary growth. In Broders' opinion, the time is not far distant when not only physicians but also the patients and their relatives, as well as life insurance companies, will be interested in the grade of malignancy of cancer. His system of standardizing histologic prognosis has been acclaimed by many surgeons throughout the country and has already influenced surgical practice. MacCarty's recent remark that a good piece of scientific observation has been spoiled by the clinician, and that clinical interpretations have gone too far, does not seem entirely justified, since Broders himself stressed the great practical value of his method. Plaut's sound criticism (1927) and his warning that the time is not yet ripe to advocate any known method of histologic grading for practical purposes have cleared the field for more extensive study.

While Ewing, Martzloff and Greenough followed Broders' system in grouping malignant neoplasms of the various organs into 3 or 4 grades of malignancy according to the relative number of undifferentiated cells present, Hueper attempted to find a more reliable index of histologic malignancy by using 20 factors pertaining to the characteristics of the parenchyma and stroma of a tumor. He used 4 principal criteria: (1) special cellular and structural characteristics, (2) characteristics of cytoplasm, (3) characteristics of nuclei and (4) characteristics of stroma, with from 4 to 6 subdivisions in each, valued from 1 to 4. The sum gave the index of histologic malignancy. Hueper emphasized, however, that the grade of histologic malignancy is certainly not the only factor on which the type of treatment should be based and the prognosis estimated. The extent of the disease as best expressed by a definite clinical grouping, the age of the patient, heredity, the general condition of the patient, the location of the tumor and its extrinsic or intrinsic qualities of growth deserve as much consideration as the histologic grading.

In his earlier studies, MacCarty had called attention to lymphocytic infiltration, fibrosis and hyalinization of the stroma as factors of prognostic value. From his clinicopathologic observations of cancer of the stomach, breast, rectum and skin he concluded that the value of these factors for determination of the clinical course of the disease could hardly be questioned. According to Ewing, well marked inflammatory reaction signifies a pronounced capacity of the organism to limit the tumor's growth, but not that the effort will be successful. He had not, he said, found the presence of lymphocytes and fibrosis a reliable sign of the outcome of the disease.

W. Fischer's and Boehmig's histologic studies on 115 nonulcerated carcinomas throw much light on the nature of stroma reactions in malignant tumors. The quality and intensity of the inflammatory changes

differed in the various areas of the same tumor so considerably that the authors warned against drawing conclusions from biopsy of small specimens. In their series, scirrhous and solid carcinoma showed much less lymphocytic infiltration than alveolar adenocarcinoma. In metastases located in the liver inflammatory reaction was never found. It was always present in early stages of cancer, while well advanced neoplasms showed only scanty local infiltration around small cell groups with active proliferation. In colloid carcinoma, the lymphocytic infiltration was absent or very small. When the tumor grew in preformed channels, such as blood vessels, lymph vessels or milk ducts, the lymphocytic infiltration was entirely missed, but it appeared as soon as the growth perforated the walls of these structures. In the opinion of Fischer and Boehmig, the stroma reaction is to be considered as inflammatory and not as specific for carcinoma; it depends no more on the structure and rate of growth of the neoplasm than on the texture of the invaded organ. The two authors would not draw any conclusions from the character of the stroma reaction on the clinical prognosis in a given case. Fischer-Wasels observed in transplanted mouse carcinoma that the lymphocytic infiltration varies widely, depending on the structure of the host organ.

Wood in 1930 stated that no one can make a prognosis from a microscopic section except in certain well recognized groups of tumors. He regarded malignancy as a clinical phenomenon, not a morphologic one. The prognosis of a neoplasm depends on many things: on the position of the growth, its relation to blood vessels, its size in some cases and the dimensions of the tumor cells wholly independent of their rate of growth.

While Wood, Ewing and Plaut recognized the great scientific and practical value of the problem of histologic grading and encouraged further investigation in this field, which still is in its infancy, Reimann regarded it as futile to decide from a small section of a tumor what will happen to a patient with cancer. According to him, in histologic grading, one attempts, by examination of the removed specimen, to determine how it grew and then to transfer this decision as a prediction of what will happen to any possible fragment left behind by the surgeon. If one is to make a prognosis at all, the presence or the absence, and the situation, of secondary tumor deposits are of greater importance than histologic grading.

The problem of grading is complicated by the well known fact that tumors of the same histologic structure, but in different locations, may have entirely different grades of clinical malignancy. Ewing in 1915 stated that carcinoma of the tongue presents a very different problem from that of carcinoma of the skin; in the alimentary tract, carcinoma increases in clinical malignancy from the anus to the lips, and also in the urinary bladder the malignancy varies according to the location, irrespective of histologic characters.

Ewing distinguished between potential and actual malignancy of a tumor. The potential malignancy can be safely estimated from histologic signs of anaplasia, abundance and abnormalities of mitoses, loss of polarity and diffuse infiltrative growth of cells. The actual malignancy is influenced by many factors that may greatly alter the course of the disease; for instance, the position of the tumor, hemorrhage, bacterial infection. Ewing pointed to the danger of relying exclusively on histologic data in forming a clinical prognosis, especially if more significant features such as gross anatomy of the tumor, condition of the lymph nodes, age of the patient, duration of the disease and other clinical aspects are thereby neglected.

MacCarty, in his latest paper on histologic grading, which differs strikingly from his former dogmatic contributions and reflects the wholesome influence of the criticism by Plaut, Reimann and Wood, admitted that all grading of cancers should be considered as in the investigative or experimental stage, and that the immature clinical utilization of scientific observation will only discredit and impede its rightful progress. He warned against using for practical prognosis the facts which he and Broders had presented, and urged that any system of microscopic grading of cancer cannot be of accurate value without many other factors being taken into consideration. There are according to MacCarty at least 15 factors governing prognosis in cancer. The most important consideration, more important than any microscopic criterion of degree of malignancy, is whether metastases are present in lymph glands or other organs, and secondly whether the surgeon could remove the growth radically.

Warthin pointed out that all degrees of anaplasia may be found in a single neoplasm, so that one's grading of malignancy will vary in a given case according to the part of the tumor from which the piece examined is taken. The questionable value of histologic grading from biopsy of small specimens, with regard to the variation of cell characteristics and stroma reaction in different areas of a tumor, is evidenced by the study of Martzloff. In 70 cases of cervical cancer, he compared material taken for biopsy with the remainder of the removed uterus, and found that in one third of the cases studied histologic examination of the biopsy material failed to show the predominant type of cancer cells as presented in the remainder of the organ. In his opinion, material taken from cervical carcinoma for biopsy will give a more or less inaccurate impression of histologic features in regard to the grade of potential malignancy.

Stewart and Spies, on the other hand, concluded from their examination of rectal carcinoma that small biopsy specimens are sufficient for the histologic grading. Having had the opportunity in 46 cases to obtain more than a single specimen from the same tumor, they found

that changes in the histologic character do not occur sufficiently often in the course of rectal cancer to interfere seriously with the prognosis as suggested by the grade given at the time of the first biopsy. In a total of 102 repeated biopsies but 10 changes in grade were made, all except 1 of these consisting in an advance of the grade.

Von Hansemann was of the opinion that in metastatic tumors there are as a rule increased anaplasia and more rapid growth as compared with the primary tumor. According to recent investigations, however, the preservation of the structural types in metastases seems much more common, and in a few cases the grade of histologic malignancy appears even to be lowered, an observation which it is difficult to understand from the clinical point of view. Patey and Scarff studied 163 cases of carcinoma of the breast for the purpose of comparing the histology of the primary tumor with that of the metastases. In 83 per cent, the secondary deposits in the lymph glands were similar in appearance and in histologic malignancy to the primary growth. In 16 per cent, however, the malignancy of the glandular metastases was lowered, and in only 1 case was it raised. Mills, Broders and Caylor found irreconcilable variation between the grade of the primary malignant tumor and that of the metastatic growth in 32 of 207 cases. In 17 metastases, the histologic grade of malignancy was lower than in the primary tumor, and the authors observed a tendency for some carcinomas to become "a little less malignant" when they became implanted in the lungs—a statement that must arouse still greater skepticism as to the clinical value of purely histologic grading.

There are many statistics in the literature that seem to speak in favor of the histologic grading of malignant tumors in different locations of the body. A systematic analysis, such as that made by Plaut on Broders' tables, may prove, however, that most of these statistics are not without fallacy. There is particularly one point which appears to me worthy of mention and which must have a deciding influence on these figures: the uncertainty of present histologic methods in differentiating the earliest stages of carcinoma from harmless atypical cell proliferations. If the latter are listed in the statistics as cancer of low grade, an entirely wrong conception of the clinical course of the different histologic types must be induced. Broders, for instance, included in his group 1, of carcinomas of the bladder, tumors that most pathologists call benign papillomas. His group II would probably fall in Aschner's class of papilloma with malignant cell groups. Then one readily understands that his classes III and IV are really malignant ones, since they are the only tumors of the bladder that are called carcinomas by most histologists. White and Weidman reported atypical epithelial proliferations on the edge of cutaneous ulcers which were graded by noted pathologists as grade I and grade II carcinoma, but which healed

promptly after conservative treatment. The difficulty of differentiating by histologic study the first stages of carcinoma of the breast from harmless atypical proliferation in chronic cystic mastitis is well known, and accounts for the everyday experience that one pathologist will seldom agree with another on the significance of the pathologic pictures in these borderline cases.

In carcinoma of the uterus, most of the efforts to establish a close relation between structure and prognosis have been announced as comparative failures. In Frank's opinion, so many incalculable factors come into play that no prognosis can be based on the histology only. Also Schottländer and Kermauner concluded from their extensive studies that the results of grading give little encouragement so far as prognosis is concerned from the examination of diagnostic excisions or curettages. R. Meyer distinguished different grades of cervical carcinoma for clinical purposes, because the unripe types are thought to respond more readily to irradiation, but he emphasized that the histologic grading of these cancers is extremely difficult at best and depends too much on the personal interpretation of the diagnostician. In his material, the unripe forms were extremely rare, and he did not see any close relation between the grade of cell differentiation and the clinical course, except that the ripe carcinomas in early stages seemed to grow more superficially, while the unripe types had often the tendency to invade the deeper structures from the beginning. But Meyer raised the question whether the density of the inflammatory stroma is perhaps not more responsible for the different direction of growth than the maturity of the tumor cells.

Lenczewski investigated the microscopic structure in 26 cases of cervical carcinoma; 12 of the patients were alive three years after operation and 14 dead. There was no relation between histology and prognosis in his cases, and the length of survival in any case seemed to depend mainly on the patient's general condition and clinical picture before treatment.

Martzloff applied his system of histologic grading to 145 cases of epidermoid carcinoma of the cervix, distinguishing spinal, transitional and spindle cell forms. In the spinal cell group there were 53.3 per cent with five year cures. In the transitional cell group—the most common variety—the occurrence of five year cures was 43.3 per cent and 34.3, respectively, in the patients operated on by the vaginal or abdominal route. Of 17 patients with the spindle cell cancer, the least common variety, only 1 was living after five years. Plaut, who applied Martzloff's method to his material at the Woman's Hospital, New York, could not find any relation between the type of cells and the outcome of the disease, with the exception of an increased number of survivals in cases with intensive hornification and a rapidly fatal outcome in those

with very irregular pleomorphic pictures. No tumors in Plaut's material could be classified as spindle cell cancers, and furthermore the cell forms in cervical carcinoma were so manifold that they did not permit establishment of a few histologic groups. He concluded that at present the clinical features are a much better guide to prognosis than the cytologic grouping.

Neither was Taylor able to find a definite relationship between histologic structure and prognosis. He applied the original method of Martzloff to 128 cases of cervical cancer. The greatest number of surgical cures occurred in tumors of grade III. The prognosis in 60 hysterectomies for carcinoma of the uterine body depended largely on the degree of gross extension at the time of institution of therapy. Also, in ovarian carcinoma, the histologic type apparently made little difference in the prognosis.

Hueper based his method of grading on 20 different histologic criteria, and 48 known end-results among 122 carcinomas of the cervix convinced him of the usefulness of his system. In group I, with a malignancy index between 22 and 39, there was unfortunately no case with a known end-result; in group II, with a malignancy index of from 40 to 54, three year cures were obtained in 61.5 per cent; group III, with a malignancy index between 55 and 69, had cures in 28.6 per cent, and group IV, with a malignancy index between 70 and 84, had not a single cure.

In McNamara's 300 cases of cervical carcinoma, the classification according to the technic of Martzloff did not harmonize with the end-results except in a few instances. Therefore he distinguished only 2 classes, that of low and that of high malignancy. In the low malignancy class he included all cancers that tended toward keratohyaline formation with pearls, the cells resembling the normal stratified squamous epithelium of the portio vaginalis. Of patients whose cancers he classified as belonging to the highly malignant group, all were dead from the disease after a three year period, while of those whose tumors were of the low grade all were living except 3 who died from other causes. The type of treatment showed little difference as regards end-results. Since McNamara grouped his material as only 15 cases of low and 276 of high malignancy, leaving almost 95 per cent of the cases unsorted, it seems questionable whether this new system will find followers.

Warren studied the problem of histologic prognosis on autopsy material and took the power of a tumor to metastasize as an index of its degree of malignancy. His 102 cases of cervical carcinoma were divided into 3 groups on the basis of differentiation of the tumor cells, frequency of mitosis and relation of tumor parenchyma and stroma. Of epidermoid carcinomas of grade I, 57 per cent had no metastases as

revealed by autopsy; of tumors of grade II, 23 per cent were without metastases, and of those in the last group all had metastasized. Warren held that in cervical carcinoma there is a close correlation between the histologic degree of malignancy and the power to set up metastases.

In endometrial carcinoma, von Hansemann maintained that, in general, histologic classification does not give any guide for evaluation of malignancy. According to him malignant adenoma of the uterine body differs in no way clinically from adenocarcinoma. Mahle, on the other hand, reviewing 186 cases of carcinoma of the fundus, divided them into 4 groups according to the amount of tissue differentiation. In the cases of grade I, which showed the least departure from the normal, no deaths occurred, while in those of grade IV every patient died. Lindsae divided his cases of cancer of the uterine body into 2 groups, adenoma malignum and adenocarcinoma. In the first, the polarity of the epithelial cells was maintained everywhere, while in adenocarcinoma definite loss of polarity and infiltration of the stroma by solid cords of cells were observed. In his 23 cases of adenoma malignum there were 12 three year cures and only 2 patients died, while in the 30 cases of adenocarcinoma there were 4 three year cures and 21 patients died. These different results were not due to differences in treatment.

R. Meyer held that in adenomatous uterine cancer, the insensible transitions between different types—not only from case to case, but also in different areas of the same tumor—do not permit a distinction between malignant adenoma and adenocarcinoma. The texture of the stroma, the presence or the absence of inflammatory changes and other factors may alter the histologic structure of a tumor considerably without changing its growth capacity.

In 1922, Sistrunk and MacCarty published a paper based on the study of 218 breasts that had been radically removed for carcinoma. They found that the greatest combined factors controlling longevity after operation were cellular differentiation and hyalinization of the stroma. According to Flothow, who studied 222 cases of mammary cancer, hyalinization of the stroma is the most effective of the tissue reactions and constitutes a practically impassable barrier to the advance of malignant cells. Lymphocytic infiltration, which is the first reaction to appear, is regarded by him as the least important defensive factor.

Greenough, however, basing his opinion on 73 carcinomas of the breast, could not confirm the view that round cell infiltration and hyalinization of the stroma are an indication of the resistance of the individual against cancer. In his belief, round cell infiltration is called forth by the presence of degenerative products in the tissues, and hyalinization is rather a factor of age or previous condition of the mammary tissue. Greenough considered the presence of marked secretory activity with droplets of mucoid secretion as an indication of low

malignancy and its absence as that of a lesser degree of differentiation. A marked variation in size of cells and nuclei combined with hyperchromatosis and large numbers of irregular mitoses carries in his opinion a grave prognosis. Greenough divided his 73 cases of carcinoma of the breast into 3 groups, of low, medium and high malignancy. Of the 19 carcinomas belonging to group I, 82 per cent were cured, including 4 with involvement of the axillary lymph glands. In the third group, 16 cases had axillary deposits and 5 had none; all patients belonging to this group died of cancer. The author felt justified in considering the determination of the degree of malignancy to be reasonably accurate and to be of prognostic value in cancer of the breast.

Siemens grouped 67 cases of carcinoma of the breast as carcinoma solidum, scirrhous, adenomatous and medullary carcinoma. There were many transitions, especially between the first, second and third groups. The metastases in the lymph glands, which were present in 74 per cent of all cases, were mostly of medullary character, and only occasionally did they represent scirrhous or adenomatous structure. Siemens found the best operative results in adenomatous carcinoma and the poorest in the medullary type, but in his opinion the histologic analysis of a tumor of the breast does not permit a reliable clinical prognosis. Also Reinecke concluded from a comparison of the histologic types after healing among 99 amputations of the breast that the morphologic variation of the malignant epithelial proliferation is of relatively little prognostic significance. Still more skeptical was Reimann after studying 100 carcinomas of the breast. He based the histologic classification on the size and staining reaction of the cancer cells, the proportion of mitoses, the architecture of the tumor, the invasion of lymphatics and blood vessels and the reaction of the stroma. The prognosis thus arrived at was compared with the actual malignancy as determined by a follow-up of the patient. It proved to be wrong in 50 per cent of the cases. Reimann therefore contended that a prognostic classification based on mathematical grading of histologic characteristics is not much better than the impression of the degree of malignancy that the experienced pathologist receives from his usual histologic examination.

Van S. Smith and Bartlett studied 234 cases of malignant tumors of the breast. They believed that the determination of the degree of malignancy is most difficult at best, for it is rare to find a mammary tumor the cells of which are homogeneous throughout. Usually pictures of varying malignancy can easily be found in the same tumor, and frequently a metastasis has an entirely different appearance from that of the primary growth. Late recurrences may not have the slightest resemblance in degree of malignancy to the primary tumor.

Williams, Lange, Kaufmann and Ewing agreed as to a lower degree of malignancy of colloid cancer of the breast, while others like Depres,

Bertrand and de Nagy stated that the presence or the absence of mucus is not a factor in the postoperative prognosis. According to Cheatle and Cutler, the clinical course of tumors exhibiting gelatinous degeneration is determined chiefly by the properties of the epithelial elements which they contain and does not depend on either the presence or the extent of the colloid material. Four of their cases of colloid cancer of the breast were among the most malignant that can be encountered. In examining whole sections of the removed breast, they were able to discover gelatinous degeneration in tumors in which, from gross appearance, its presence was unsuspected.

Lee and Stubenbord were of the opinion that cases of carcinoma of the breast may be graded from purely clinical data more accurately than the histologic study can reveal. In 100 primary operable cancers of the breast, the authors estimated the degree of malignancy according to 4 clinical features, namely, age, presence of lactation, rate of growth and extent of the disease. Of their patients grouped in grade A, 69 per cent were alive and well after five years; group B showed 34 per cent and grade C 4 per cent surviving the five year period. This study is of especial interest because the same 100 cases were graded by Ewing solely on histologic criteria; 52 per cent of the patients who presented his grade I tumors were without evidence of the disease five years after operation, while among those with tumors of grade II and grade III there were 33 and 29 per cent, respectively, surviving the five year period. The divergence between the different histologic groups should be much wider to have the histologic grading of any significance. The tumors of 10 patients remaining well and alive were classified in the clinically benign group, but on a histologic basis these were placed in grade II. Of the highly malignant clinical group of cancers 9 in patients who succumbed to the disease within one year were classified as grade II on histologic criteria. It seems fair to conclude that the clinical grading made a more accurate selection of the patients than did the microscopic method.

To exclude the possible influence of differences in treatment on the clinical course, Daland made a study of untreated mammary cancer in 11 cases which came to autopsy. With the assistance of Greenough, the tumors were graded according to their histologic malignancy. None could be placed in group I; 6 were grouped in the second and 4 in the third group. Daland was unable to demonstrate a slower clinical course of the disease in the cases of lower potential malignancy. The location of the tumor appeared to him of greater significance in determining the length of life than the degree of histologic malignancy.

Snoke observed that cutaneous cancer of the face, in different locations, pursues a course independent of the cell type, and that anatomic factors, especially underlying bone, cartilage or fascia, may increase

the malignancy of a tumor regardless of cell differentiation. In his opinion, the histologic picture is only one aspect of the disease and at present an overemphasized one.

From his study of 319 cases of buccal carcinoma, Phillips concluded that a well marked correlation exists between the histologic character and the clinical course of buccal carcinoma, and that the usefulness of Broders' system of histologic classification has been amply demonstrated. Also Jorstad, after comparing histologic malignancy and clinical course in 200 cancers of the lip and oral cavity, felt that grading of carcinoma is of enough significance for its practice to be continued. The differences of longevity between Jorstad's histologic groups, especially his first, second and third, seem to me not so impressive as to justify his confidence in histologic grading; there were five year cures in 80 per cent of the first group, 76 per cent of the second and 60 per cent of the third. The clinicians of the Memorial Hospital, New York, judged that the histology does not aid in the selection of the treatment for cancer of the lip to the same extent that it does for cancer of the oral cavity proper, and that recognition of the clinical type of disease is of relatively greater importance. Neither did Fischel believe that as yet the histologic form of either the primary tumor of the lip or the metastases should influence the plan of surgical treatment. He would apply the most thorough local destruction of the tumor, followed by an equally thorough dissection of the neck, no matter what the histologic grade may be.

The periods of survival after the first symptoms which Clayton observed in 39 cases of squamous cell carcinoma of the esophagus do not place any significance on histologic classification of tumors in this location. The duration of disease after onset of the first clinical signs was, in his first group, sixteen months; in the second group, eight months; in the third group, five months, and in the fourth group, three and one-half months.

Grading according to morphology seems to apply fairly well to epithelial tumors of the larynx. A series of Thomson's cases of laryngeal carcinoma gave, in group I, 6 per cent, and in group IV, 72 per cent recurrences.

Konjetzny studied the end-results of gastric resection, to determine the relation of the histologic picture of carcinoma of the stomach to the clinical prognosis. He did not obtain decisive results, as there does not exist, in his opinion, a nomenclature for all the various histologic types of gastric carcinoma; furthermore, mixed forms of cancer occur frequently, the grading of which will differ widely according to whether only a single small portion of the tumor is examined or the whole specimen. Konjetzny arrived at the conclusion that there is little prospect of being able to determine with certainty the grade of malignancy of a given gastric carcinoma from the histologic picture

alone, and that the gross behavior of a gastric tumor is of greater significance. Also Brodnitz, Finsterer, von Haberer and Weil were unable to find any definite relationship between cell type and clinical prognosis in gastric carcinoma, while Scott expressed the belief that a slightly longer survival of the group showing the greatest cellular differentiation can be demonstrated.

Rankin and Broders graded 598 cases of carcinoma of the rectum in accordance with the principle of cell differentiation. The percentage of cases in which metastases were present rose in direct proportion to the grade of malignancy. The percentage of good results after operation decreased in inverse proportion to the grade of potential malignancy, and in cases of carcinoma graded III and IV without demonstrable metastases, the end-results were not much better than in cases of carcinoma of grade I that were accompanied by metastases. In colloid carcinoma of the rectum, Rankin and Chumley found a tendency of the amount of mucus present to be inversely proportional to the grade of malignancy, except in the cases of highest malignancy in which 58.3 per cent showed the highest observed grade of mucus formation. The authors admitted that this fact is not in accord with the view that mucus is a sign of cell differentiation. Furthermore, they found the clinical prognosis in colloid carcinoma unfavorable regardless of the grade of malignancy or the amount of mucus present if the lymph nodes were involved. Miles stated even that colloid carcinoma of the rectum is extremely malignant and is apt to recur after the most radical operation.

Bell regarded the two-stage abdominoperineal operation as the method of choice in rectal carcinoma when the grade of malignancy is high and when the physical condition of the patient permits this serious surgical intervention. Carcinomas of grades I and II, when near the anal margin, can be safely dealt with by colostomy and posterior resection, with an expectancy of life comparable to that offered by the abdominoperineal method without its high operative mortality.

Aschner did not believe that in tumors of the bladder prognosis can be made correctly from biopsy material and classification be based safely on cell grading alone. He regarded the presence or the absence of infiltration of the wall to be a more reliable guide to the gravity of the situation. The site of the malignant tumor also influences prognosis materially, since it determines its resectability. Hunt's observations were based on 370 treated patients with carcinoma of the bladder: Irrespective of the size and situation of the tumor or the magnitude of the operation, 65 per cent of those who had carcinoma of grades I and II lived three and more years without recurrence, as compared with 34 per cent of those who had carcinomas of grades III and IV. When the results were determined according to the sites of the tumors, he found

that those following operations on the base of the bladder were 50 per cent worse than those following operations for lesions in the lateral wall and dome of the bladder, irrespective of the grade of histologic malignancy.

According to Kolodny, the attempts of pathologists to form the prognosis of a tumor from its morphologic features alone has nowhere failed more than in tumors of the bone. The histologic structure is merely a link in the whole chain of circumstances that render a tumor malignant. In this chain much depends on purely clinical evidence. Age, rapidity of growth, situation, size of the tumor, encapsulation and vascularity are of the greatest importance in making a valuable prognosis in a given case.

Phemister presented 5 cases of undifferentiated round cell sarcoma of bone that proved to be exceptions to the generally accepted teaching that the less differentiated the cells the more malignant the tumor. Cures were obtained in all these cases, lasting from four and two-thirds to ten and three-fourths years.

The histologic grading of tumors of the brain is, according to Bailey and Cushing, of the greatest practical value. The cerebral gliomas, which represent about 42 per cent of all intracranial new growths, have heretofore been generally regarded as hopelessly malignant tumors. Impressed by the fact that many patients with tumors of this sort have survived for unexpectedly long periods of time after incomplete extirpation of the lesion, Bailey and Cushing undertook a reclassification of their cases, and they adopted for the gliomas a terminology consistent with that used for the histogenesis and normal structure of the brain. They subdivided their 254 gliomas into 13 categories, and found that the tumors in which the cells reproduced the structure of the less differentiated cells in the developing nervous system were more actively growing than were the ones composed of more highly differentiated cells Almost half of their gliomas were of the latter sort and may be regarded —apart from the mischance of their occupying an inaccessible position in the brain—as comparatively benign lesions.

The successive groups of Cushing's newly classified gliomas when arranged in series according to the average periods of survival of the patients show a variation from those that leave the patient few months of life to others that, when properly treated, permit the patient to survive ten years or more. And this lengthened period goes hand in hand with the increasing degree of differentiation of the neoplastic cells. Bailey and Cushing concluded that no less important than the localization of tumors of the brain and technical methods is a clear understanding of the life history of the lesions treated, because on this more than on anything else depends the nature of the surgical intervention appropriate to the particular kind of tumor that happens to be disclosed.

In spite of the large volume of work that followed the pioneering of Broders, it must be said that the problem of histologic grading of cancer is far from being solved, and that its practical value is still very limited. The present knowledge of the relationship between histology and prognosis has been well summarized by Barnard: "A competent histologist can say of a tumor that it is a type which grows rapidly or slowly, and he may be able to add that it usually produces metastases early or late in its growth. But it is not yet within his power to draw a graph of malignancy indicating the expectation of life to be associated with each shade of variation to be found in malignant tumors."

IV. HISTOLOGIC CHARACTER AND RADIOSENSITIVITY OF TUMORS

Modern radiotherapy of cancer has its scientific foundation in the theory that neoplastic cells have a greater radiosensitivity than resting tissue cells. Cancer cells are thought to vary in their radiosensitivity in much the same way as normal cells, but knowledge of the relation between histologic character and response to irradiation is still rudimentary.

Perthes (1903) was the first to associate the radiosensitivity of a tissue with its reproductive activity, basing his belief on clinical observations and experimental studies. In 1906, Regaud and Blanc deduced from their experiments with testicles that in the life of a cell the stage of karyokinesis is the time of least resistance to irradiation. Later in the same year, Bergonié and Tribondeau from their observations of human tumors and experiments with rat testicles derived the general law that the greater the reproductive activity of cells, the more prolonged their process of karyokinesis and the less definitely fixed their morphology and their functions, the more intense is the action of the x-rays on them.

Recent histologic observations on irradiated tumors seem to substantiate the much defended view that irradiation acts by direct destruction of cells. Waetjen studied 4 squamous cell carcinomas of the uterine cervix in patients who died from one to six days after the application of radium. The earliest process noted after irradiation was a cessation of mitosis in the tumor cells; then the nuclei of the cells revealed evidences of degeneration, and finally the entire cells became necrotic. The stroma reaction—infiltration with leukocytes—appeared to be secondary to the changes in the tumor parenchyma. Gambarow also noticed in irradiated tumors primary degenerative changes in the cancer cells and secondary proliferation of the connective tissue. The nuclei in resting cells showed much less intensive changes than occurred during cell division. On 200 specimens of tissue obtained for biopsy in 30 cases of cervical carcinoma before, during and after irradiation, Fedorejeff was able to corroborate these observations. In the nuclei of the cancer cells

swelling, vacuolization, karyorrhexis and karyolysis occurred on the first day. Later the mitoses disappeared, but reappeared after two or three days in degenerated form, only to disappear completely after the fifth day. These nuclear changes were followed by swelling, vacuolization, hyalinization and lysis in the cytoplasm, leading to complete necrosis of the tumor cells. Inflammatory changes in the stroma and scar formation, hyaline degeneration and thrombosis of blood vessels were constant findings in the later stages.

Physiologic studies on tissue cultures by A. Fischer suggest that by irradiation growth-restraining substances are liberated from the cells. The effect of irradiation on resting cells was latent, manifesting itself only after the cells were forced to cell division.

When one attempts to apply the laws of radiosensitivity clinically, a definition of radiosensitivity is necessary in the first place. Two distinct phenomena are involved that do not parallel each other, namely, the primary regression of a tumor following irradiation and the definite cure. A thorough study of lymphosarcomas of the neck by Spies indicates that the more prompt and the greater the primary reduction of the irradiated tumor, the less time will the patient survive. In all of his 261 cases followed to the end, there was a probable mortality of 100 per cent. Lymphosarcomas, however, are generally regarded as models of radiosensitivity. By a definite cure is usually meant one that has lasted for at least five years. The published statistics of radiotherapy in which five year cures are related to morphologic characters of tumors are few. Furthermore, attempts to classify cancers from biopsies of small pieces of tissue into more or less radiosensitive groups are often fallacious, because examination of a small specimen obtained from the surface may not reveal the histologic characteristics of a given tumor varying in its different parts.

Ewing observed variations in grade of potential malignancy and in radiosensitivity in tumors from all parts of the body, less marked in tumors of the skin than in those of mucous membranes. According to him, response to irradiation usually runs parallel with the degree of anaplasia and potential malignancy, but by no means always. For instance, in the skin, basal cell carcinoma is relatively benign, but radiosensitive, while melanoma is highly malignant, but very radioresistant. Although in tumors of lip and tongue considerable variations in clinical malignancy occur, with corresponding changes in structure, most of these carcinomas are resistant to irradiation. The desmoplastic property of many epidermoid carcinomas is one of the most important factors in rendering them resistant. As a rule the more adult the cell type, the more active is the stroma reaction. On the other hand, the highly anaplastic and rapidly growing cellular tumors excite little stroma reaction and may be completely destroyed by external irradiation. Vascularity is

regarded by Ewing as one of the most important factors in the destruction of tumors by irradiation. Bulky papillary carcinomas melt away rapidly, mainly because the delicate blood vessels are destroyed. The location of the tumor has an important influence on the result of irradiation. In bone it is extremely difficult to destroy epidermoid carcinoma, because the inflammatory reaction is poor; fat tissue also is a very unfavorable bed for the treatment of most carcinomas. Ewing presented the factors entering into radiosensitivity in a table, which offers a provisional estimate of their importance. He listed as the most significant: embryonal quality and anaplasia of the cells, desmoplastic property, texture of the bed of the tumor and general condition of the patient. Also Haagensen emphasized that the constitution of the patient, local conditions and factors inherent in the tumor must be considered in an estimation of radiosensitivity, and that the phenomenon of radiosensitivity is a great deal too complex to be envisaged by a simple statement of one or two factors.

Epidermoid carcinomas are, in Regaud's opinion, the only epithelial tumors that are cured by irradiation almost as a routine. Since the time of Darier (1904) it had been believed that carcinomas of the skin could be divided into radiosensitive basal cell carcinomas and resistant squamous cell cancers. Regaud found that the sensitivity of both varieties of cancer is the same; similar end-results of treatment of the basal cell and squamous cell types by the same technic showed that the older view was incorrect. This fact does not contradict, however, the experience that it is more difficult to obtain a clinical cure in squamous cell carcinoma than it is in basal cell cancer. In the former, the early invasion of the deeper tissues makes it much more difficult to reach all involved parts, whereas in the latter the entire disease is usually superficial and of slight extent.

The most frequently quoted paper supporting Bergonié's law that the radiosensitivity increases with the degree of immaturity of tumor cells is the study by Healy and Cutler. They distinguished among 200 cases of carcinoma of the cervix 3 groups: (1) the adult type with hornification and occasional pearl formation; (2) the plexiform type with large, partially differentiated tumor cells and (3) the anaplastic type with small round or spindle cells. In advanced cancer of the cervix the end-results after radiotherapy were extremely poor when the neoplasm was of the adult type and unexpectedly favorable when it was of the anaplastic type. In the early stages of the disease, the cures were comparatively high, regardless of cell type. Healy and Cutler concluded from their studies that the clinical stage at which the treatment is instituted and the type of the cancer cells are the most important factors in clinical prognosis when radiation is employed.

Bowing and Fricke stated that their experience with 625 cases of cervical cancer is in accord with the view of Healy and Cutler, but, in my

opinion, their statistical data are not convincing in regard to the prognostic value of histologic grading. The rate of survival of patients with tumors of their grade II was 52.9 against 54.99 per cent of those with tumors of grades III and IV. Thibaudeau and Burke concluded from their investigation of 28 cases of carcinoma of the cervix in which the patients were alive and well five years after roentgen treatment, that histologic grading does not give any information about radiosensitivity.

Schmitz and Hueper also were unable to demonstrate the validity of the law of Bergonié in tumors of the uterine cervix and of the breast. While the primary effect of irradiation on highly immature tumors may be grossly more marked than that seen in well differentiated carcinomas, the permanent curative results obtained in undifferentiated cancers were poorer than those seen in the mature types. Schmitz and Hueper expressed the belief that the degree of histologic malignancy is of the same significance in regard to prognosis in radiotherapy as it is in surgery.

Doederlein classified 275 irradiated cervical cancers into undifferentiated, moderately differentiated and well differentiated histologic groups. The degree of differentiation among the squamous cell carcinomas played practically no rôle in their response to irradiation. According to Lacassagne, the radiosensitivity of an epidermoid cancer of the uterine cervix cannot be forecast from a consideration of the size and form of the tumor cells, the number of mitotic figures, the stroma reaction or the condition of the blood vessels. Histologic observations do not explain, in his opinion, why some very extensive cancers of the cervix can be cured in spite of insufficient roentgen treatment, while others of very limited extent recur in spite of proper treatment.

In buccal carcinoma, Phillips did not find any direct relationship between histologic character and response to irradiation; the highly differentiated carcinoma reacts to radiotherapy as well as the very anaplastic types. Quick and Widmann, on the other hand, stated that in this location radiosensitivity depends on cellular differentiation. Stewart found cancers of the oropharynx more radiosensitive than those located in the anterior portion of the buccal cavity, in spite of similar histologic structure. Rather adult epidermoid carcinoma, situated in the pharynx, may be as radiosensitive as the rapidly growing anaplastic lympho-epithelioma of this region (Haagensen). Lacassagne's observations also signify that in oral cancer the clinical cure depends not less on the anatomic site of the tumor than on the histologic character. His end-results in cancer of the floor of the mouth were poorer than those obtained in carcinoma of the tongue, in spite of the fact that the former was composed of more immature cells.

There seems to be general agreement that adenocarcinomas of different organs are not amenable to irradiation. This failure of roentgen

therapy is apparently due not only to difficulty in reaching the deeper parts of the tumor and to early invasion of regional lymph glands, but to inherent radioresistance. Regaud explained this resistance by the biologic fact that, in general, a cell is scarcely, if at all, radiosensitive when it is in secretory activity. The difference in radiosensitivity of epidermoid and glandular carcinoma was clearly demonstrated by Windholz. He had the opportunity to examine histologically a uterus in which a squamous cell carcinoma and an adenocarcinoma were situated close together. While the epidermoid carcinoma showed marked degeneration, the glandular tumor was only slightly affected by irradiation. Regaud stated that he had never succeeded in curing a case of adenocarcinoma of the uterus by short wave irradiation. Also the sensitivity of rectal adenocarcinoma is generally feeble; the few authentic cures of rectal carcinoma have apparently been obtained by methods of diffusely caustic radiotherapy. In interesting contrast to Regaud's statement are the observations of Bowing and Fricke that adenocarcinomas of the uterine cervix of all four histologic grades appeared to have a better prognosis after irradiation than the squamous cell types. In Doederlein's experience, the glandular carcinomas of the corpus were more radiosensitive than those of the cervix. Eleven of his 17 patients were alive and well after five years, and the histologically riper forms were associated with a higher rate of survival than the unripe forms.

Owing to the confusion in the classification of the various forms of mammary cancer, the knowledge of their radiosensitivity is extremely meager. According to Lacassagne, certain cases are amenable to radiotherapy while others withstand the most vigorous irradiation, and yet up to the present histologic differentiation between these two varieties is unsuccessful. Metastases of mammary carcinoma in lymph glands and recurrences in the skin disappear often promptly after irradiation, while the primary tumor of the breast does not respond to this form of treatment. It seems probable that the reaction of tumor tissue to irradiation depends as much on such factors as blood supply and character of the stroma as on the inherent qualities in the cancer cell itself (Lee). Pfahler regarded histologic grading of tumors of the breast as of no aid in the determination of the prognosis when irradiation is employed.

As a result of unsatisfactory results of surgery in cancer of the thyroid gland, irradiation is more and more applied in the treatment of these tumors. Haagensen and Clute and Warren agreed that the less rapidly growing and less anaplastic types, especially adenocarcinomas, are moderately radiosensitive, while the highly anaplastic types are not affected by irradiation. In this particular group of tumors, the law of Bergonié and Tribondeau has therefore no validity.

Reviewing the literature on histologic character and radiosensitivity of tumors, I can only repeat the statement of Plaut in 1927, that there

is a bewildering mass of contradictions and misunderstandings in a matter of greatest theoretical and practical importance. Further knowledge must come through painstaking analysis of particular groups of tumors. As Wood pointed out at the Cancer Symposium of the Radiological Society in 1930, the great clinics of this country, which have a large choice of material at their disposal, owe to the medical profession, and through it to humanity, the publication of mass statistics that will include not only complete clinical histories and five year results, but also photomicrographs of all individual types of cancer. Such a complete and detailed atlas, demonstrating the relation between morphologic characteristics and radiosensitivity on several thousand tumors of one particular kind, would be appreciated by pathologists throughout the world as a real contribution to the ultimate conquest of cancer.

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Notes and News

DOCTORATES IN BACTERIOLOGY AND PATHOLOGY GRANTED BY AMERICAN UNIVERSITIES, 1931-1932

Clarence J. West and Callie Hull, Research Information Service, National Research Council, Washington, D. C.

BACTERIOLOGY

Brown: Merrill Wallace Chase, "Further Studies on the Liberation of Toxins from Salmonella Schotmuelleri Principally by Repeated Freezings and Thawings." Robert Merrett Pike, "Toxic Substances Produced by Staphylococci Grown on Solid Media with Special Reference to the Depression of Phagocytosis by Staphylococcus Filtrates."

California: Claude E. ZoBell, "Cultural Requirements and Metabolism of the Brucella Group."

Chicago: William Burrows, "The Nutritional Requirements of Clostridium Botulinum." Leo Philip Doyle, "I. Serum Reactions Produced by Feeding Antigens. II. The Length of Survival of Paratyphoid Bacilli in Foodstuffs." Carl Oswald Lathrop, "Biological Studies of Pathogenic Strains of Bacterium Coli from Human Sources." Einar Leifson, "Bacterial Spores." Bertha Kaplan Spector, "A Comparative Study of Cultural and Immunological Means of Diagnosing Infections with Endamoeba Histolytica."

Columbia: Margaret Holden, "The Nature and Properties of the Virus of Herpes."

Cornell: Herman Jacob Brueckner, "Primitive or Filtrable Forms of Bacteria and Their Occurrence in Milk." Clifford Darton Kelly, "Chemical Changes in Cheddar Cheese in Their Relationship to the Lactic Acid Streptococci." Clair Eugene Safford, "The Occurrence and Numbers of Primitive Forms of Bacteria in Nature and in Pure Culture." Abdel Magid Wahby, "Growth of Pathogenic Bacteria in Milk."

Iowa State College: Dean Albert Anderson, "The Production of Gum by Certain Species of Rhizobium." Harry E. Goresline, "Studies on Agar-Digesting Bacteria." Ralph Victor Hussong, "The Relationships of a Lipolytic Organism to Rancidity of Butter." John Albert Nelson, "The Correlation Between the Organisms Found Microscopically and the Bacterial Deterioration of Butter." Harold Cecil Olson, "The Microflora of Churns and Its Importance in the Deterioration of Butter." Roger Patrick, "The Fermentation of Levulose by Some Bacteria of the Genus Aerobacillus." Arthur Wesley Young, "The Winogradsky Spontaneous Culture Method for Determining Certain Soil Deficiencies."

Johns Hopkins: Eric Christian Gilles, "The Isolation of Tetanus Bacilli from Street Dust." Eloise Elaine Greene, "A Study of Spirochetes in the Cat, with Special Reference to Those of the Alimentary Tract."

Massachusetts Institute of Technology: Marshall Walker Jennison, "A Critical Study of the Effect of Temperature upon Certain Aspects of Bacterial Growth Curves."

Michigan: Alden Franklin Roe, "Anaerobic Methods and the Dissociation of Bacillus Welchii."

Minnesota: Millard Fillmore Gunderson, "Studies on Western Duck Sickness." Milan Vaclav Novak, "Dissociation of an Actinomyces into Bacterial Forms."

Ohio State: Eva Galbreath Campbell, "A Thermophil Nitrite Former."

Pennsylvania: Bess E. Segal, "Serolobical and Cultural Studies of Meningococci with Special Reference to Type V."

Pittsburgh: Felice A. Rotondaro, "The Development of Bacteriology: Bibliography."

Rochester: Clarence Frederic Schmidt, Jr., "Studies in Bacterial Calorimetry."

Rutgers: Herbert W. Reuszer, "The Decomposition of Hemicelluloses with Special Reference to Their Uronic Constituents."

Vanderbilt: Lurline Valeria Richardson, "Diphtheria Antibodies Transmitted to the Offspring of Immune Guinea Pigs."

Washington: Ruby May Bohart, "A Study of Sensitization in Experimental Tuberculosis."

Wisconsin: Lois Almon, "The Stability of Cultures of Rhizobium." Ruby Bere, "I. Copepods Parasitic on Fish of the Trout Lake Region. II. The Effect of Freezing on the Number of Bacteria in Ice and Water from Lake Mendota. III. The Bacterial Content of Some Wisconsin Lakes." Adolph Alexander Hendrickson, "Studies on Certain Physiological Characters of Phytomonas Tumefaciens, Phytomonas rhizogenes and Bacillus Radiobacter and Their Relations to Plants." Elmer Reeve Hitchner, "A Cultural Study of the Propionic Acid Bacteria." Ernest Carr McCulloch, "The Germicidal Efficiency of Sodium Hydroxide." Harry Edvin Sagen, "Comparison of Certain Physiological Characters of Phytomonas Tumefaciens, Phytomonas Rhizogenes and Bacillus Radiobacter." William Bowen Sarles, "The Production of Volatile Acids by the Fermentation of Cellulose at High Temperatures." Chun Chieh Young, "Oxidation and Reduction of Alexin."

Yale: Agnes Roseburgh Beebe, "The Influence of Age upon the Reaction to Toxins, Especially in the Neonatal Period." Catherine Seeley Flynn, "On Variation and Filtrability of Bacillus Mesentericus and Bacillus Vulgatus." Norman Edwin Gibbons, "A Bacteriological Study of Fresh and Frozen Marine Fishes." Lawrence William Slanetz, "A Systemic Study of the Fusiform Bacteria."

PATHOLOGY

Chicago: Cornelius Albertus Hospers, "Studies in Cholesterol Metabolism: I. The Experimental Production of Gallstones in Hypercholesterolemic Rabbits. II. The Blood Cholesterol in Anesthesia." Robert Stewart Jason, "Studies on the Histopathology of the Palatine Tonsil and on the Immunological Reactions of the Adjacent Tissues." Guillermo Alfredo Pacheco, "Cellular Immunity." William Taylor Miller, "The Blood Picture in Healthy Cattle and Cattle Affected with Johne's Disease."

George Washington: Leon Stuart Gordon, "The Pathology of Intracranial Hemorrhage in the New-Born."

Johns Hopkins: Meridian Ruth Greene, "The Effects of Vitamins A and D on Antibody Production and Resistance to Infection." Pearl Kendrick, "The Antigenic Properties of Bacteriophage Lysates of Salmonella Suipestifer as Indicated by the Antibody Response in Rabbits."

Michigan State College: Leo Hansom Himmelberger, "The Significance of Lymphatic Tissue and Adenoma-Like Areas in the Thyroid Gland."

New York: Julius August Klosterman, "Studies on Experimental Spirochaetosis Icterohaemorrhagica (Weil's Disease)."

Northwestern: Dora Fishback, "Alteration of Glycogen, Lactic Acid and Phosphorus Compounds in Experimentally Produced Acute Molecular Degeneration of Skeletal Muscle."

Stanford: Denis Llewellyn Fox, "Some Chemophysical Aspects of Carbon Dioxide Narcosis in Living Cells."

Washington University, St. Louis: James Ralph Wells, "The Origin of Immunity to Diphtheria in Isolated Communities of Central and Polar Eskimos."

Western Reserve: Lyle Alfred Weed, "The Biological Properties of Certain Organic-Mercury Salts."

Yale: Leona Baumgartner, "Qualitative Changes in Antibody During the Development of Serological Maturity."

University News, Promotions, Resignations, Appointments, Deaths, etc.—Hugh K. Ward has been appointed assistant professor of bacteriology and immunology in Harvard Medical School.

Cyril N. H. Long, assistant professor of medical research in McGill University, has been appointed director of the Cox Institute for a Research in Diabetes at the hospital of the University of Pennsylvania.

John A. Kolmer has resigned as professor of pathology and bacteriology in the graduate school of medicine of the University of Pennsylvania and has accepted the professorship of medicine in Temple University, Philadelphia.

Sir Ronald Ross, the discoverer of the transmission of malaria by mosquitoes, died in London on Sept. 16, 1932, at the age of 75.

Society News.—The forty-third annual meeting of the Association of American Medical Colleges will be held in Philadelphia on Nov. 14 to 16, 1932.

The thirty-fourth annual meeting of the Society of American Bacteriologists will be held at Ann Arbor, Mich., Dec. 28 to 30, 1932.

The next meeting of the Pathological Society of Great Britain and Ireland will be held at University College Hospital Medical School, London, on Jan. 6 and 7, 1933.

Abstracts from Current Literature

Pathologic Anatomy

CARCINOMA OF THE GASTROJEJUNAL STOMA FOLLOWING OPERATION FOR PEPTIC ULCER. HARRY A. SINGER, Arch. Int. Med. **49**:429, 1932.

The reappearance of symptoms following gastro-entero-anastomosis for peptic ulcer generally indicates a benign complication or sequel. Recurrence of the old or formation of a new ulcer and nonmalignant obstruction are most frequently suspected. Occasionally, however, the clinical manifestations may be produced by a carcinoma. In one such case, that of Schwarz, a patient who had remained well for six years after gastro-enterostomy began to have symptoms of obstruction of the stoma, which were due to a malignant growth. In another case, that of Eichelter, a neoplasm by encroaching on the lumen of the stoma led to manifestations referable to obstruction of the proximal loop. In a third case, the one herein reported, the carcinoma, being polypoid, produced no clinical obstruction, but gave rise to a set of indistinctive symptoms. The presence of a palpable mass and the roentgen evidence of a filling defect within the gastric silhouette furnished the chief reasons for the preoperative diagnosis of carcinoma of the anastomosis.

FROM THE AUTHOR'S SUMMARY.

SQUAMOUS EPITHELIAL RESTS IN THE HYPOPHYSIS CEREBRI. H. T. CARMICHAEL, Arch. Neurol. & Psychiat. **26**:966, 1931.

The normal hypophyses removed at necropsy in a group of fifty-five cases were studied by means of serial sections. Masses of cells resembling squamous epithelium in histologic appearance were found in eighteen cases (32.7 per cent). In the nine subjects who were less than 20 years of age, groups of cells resembling squamous epithelium were not found. The incidence of these masses of cells, which apparently were squamous epithelium, among the forty-six adult subjects was 39.1 per cent. It seems reasonable to attribute the origin of these groups of cells, which apparently were squamous epithelium, to rests of the former hypophyseal duct, and to accept their relation to the so-called tumors of the hypophyseal duct; that is, if it is accepted that the rests cannot be identified in subjects who have not reached the age of 20 years, because at that time the cells of the rests are not sufficiently differentiated from the other epithelial cells in the neighborhood.

AUTHOR'S SUMMARY.

THE HISTOPATHOLOGY OF TRIORTHOCRESYL PHOSPHATE POISONING (GINGER PARALYSIS). MAURICE I. SMITH and R. D. LILLIE, Arch. Neurol. & Psychiat. **26**:976, 1931.

The nerve changes caused by drinking adulterated Jamaica ginger have been studied by Smith and Lillie on animals (monkeys, cats, dogs, chickens) and the results compared with those found in men. The animals were given orally, subcutaneously or intravenously various doses of triorthocresyl phosphate and were kept alive from several hours to about two months. The peripheral nerves, spinal cord and viscera were studied with numerous methods. The main changes were found in the peripheral nerves with especial involvement of the myelin; much less affected were the motor cells of the spinal cord. The lesion of the cord is considered secondary, the result either of axonal reaction or of extension of the degeneration from the peripheral nerves. The conclusions are that triorthocresyl phosphate is essentially a poison of the nervous system affecting mainly the lower motor neuron.

GEORGE B. HASSIN.

CHRONIC PROGRESSIVE SUBCORTICAL ENCEPHALITIS. FREDERIC J. FARNELL and JOSEPH M. GLOBUS, Arch. Neurol. & Psychiat. **27**:593, 1932.

A woman, aged 40, after two falls complained of pain in the back and nervousness. Eleven months later, the patient was unable to walk, lost sensations in the legs and complained of pollakiuria. The patient showed involvement of the pyramidal tracts, marked flexion of the upper and lower extremities and, in the later course of the disease, a definite picture of decerebrate rigidity. The course was rapid and progressive. Microscopic examination revealed a normal cortex, degeneration of the subcortex with foci of demyelinization, microglia and fat granule bodies filled with fat, arteriosclerosis and "almost complete general disintegration" of the blood vessels. Fat changes, "definitely pathologic," of the ganglion cells of the basal ganglions, substantia nigra and pyramidal tracts were present. In the presence of arteriosclerotic changes, the disease in question differs from Schilder's disease.

GEORGE B. HASSIN.

HISTOLOGIC CHANGES IN THE BRAIN IN FATAL INJURY TO THE HEAD. CARL W. RAND and CYRIL B. COURVILLE, Arch. Neurol. & Psychiat. **27**:605, 1932.

The authors studied the reaction of microglia and oligodendroglia to injuries of the brain — edema, contusion, laceration and hemorrhages (gross and petechial). Twenty-four cases were studied, all in human beings, with special reference to the length of time that had elapsed between injury and death and to the type of lesion. In edema, the microglia is generally not affected. In contusion, the changes in the microglia depend on the severity of the injury and its age. They may occur as early as within one hour or less. The early changes are vacuolization, mitotic and amitotic division of cells and swelling of the major cytoplasmic processes. Transitional microglial changes up to the formation of fat granule bodies were found. The authors could not form conclusions as to the difference between clean puncture wounds in experimental animals and diffuse contusions following injury to the human brain. The general course of the microglial changes is: early swelling of the major processes, or a definite swelling of the cytoplasm and all the processes, the spider cell stage, the ameboid stage and the stage of compound granule corpuscles. In hemorrhages of the brain, the microglial reaction is delayed until the red cells are destroyed. The conclusion arrived at is that the microglia have a primary phagocytic function and probably a secondary limited protective reaction.

The reaction of the oligodendroglia may be local, near the injury, but is usually general, in contrast to the microglial reaction, which is local. The early reaction shows as acute swelling, more or less uniform, in all portions of the brain. It may be prompt. It was present in a woman killed outright, and in another case within thirty minutes after injury. If the injury is not severe, the cell may be restored. Regressive changes — pyknosis and vacuolation — occur often, especially near the place of injury. Transformation into fat granule bodies was not observed.

GEORGE B. HASSIN.

FAMILIAL PROGRESSIVE MUSCULAR ATROPHY. GEORGE A. MOLEEN, W. C. JOHNSON and H. H. DIXON, Arch. Neurol. & Psychiat. **27**:645, 1932.

One of three brothers afflicted with progressive muscular atrophy was followed for over twenty years. The main clinical feature was absence of the claw hand, though the thenar and hypothenar eminences were markedly wasted. Pathologic examination twenty-nine years after the onset revealed practically normal ganglion cells throughout the spinal cord, pons and other regions, but marked degenerative changes in the peripheral nerves and muscles. In the former, the myelinated fibers were decreased in number; many were replaced by connective tissue and an increased number of fibroblasts. The nonmyelinated fibers were intact. The muscle fibers showed atrophy, some more, some less. In advanced stages, only remnants of muscle fibers were left — in the form of granular material and

particles of a hyaline substance. In early stages, the nuclei, which were small and pyknotic, were increased in number, and in later stages they formed clusters. Only insignificant ganglion cell changes were found in the spinal cord; these were in the lumbar region, and were considered to be the result of retrograde degeneration.

GEORGE B. HASSIN.

CHRONIC PROGRESSIVE CHOREA. C. DAVISON, S. P. GOODHART and H. SHLIONSKY, Arch. Neurol. & Psychiat. **27**:906, 1932.

Three cases of chronic progressive chorea (two were of Huntington's chorea and one was due to arteriosclerosis) were studied clinically and pathologically. The gross changes were: arteriosclerosis of the brain, with especial involvement of the basal ganglions and cerebellum, and atrophy of the convolutions of the brain and of the corpus striatum. In one case, the globus pallidus was shrunken. There was acute and chronic cell disease in the third, fifth and sixth cortical layers, involving small and to a lesser extent large ganglion cells of the neostriatum. In one case, demyelinization of the white fibers of the frontal and temporal lobes was present. The rostral portion of the caudatum was more involved than the caudal. The combination of cortical and subcortical (neostriatal) changes in the three cases speaks for a complex mechanism of the involuntary movements in progressive chorea.

GEORGE B. HASSIN.

LISSAUER'S DEMENTIA PARALYTICA. H. HOUSTON MERRITT and M. SPRINGLOVA, Arch. Neurol. & Psychiat. **27**:987, 1932.

In eight cases of atypical dementia paralytica (Lissauer's form) there occurred epileptiform and occasionally apoplectiform attacks, which were followed by hemiplegia and aphasia. Microscopic changes were present in the cortex, which showed outspoken atrophy not so much in the frontal as in the temporal and inferior parietal lobes. Changes were also present in the basal ganglions and the subcortical white substance. Of other microscopic changes, the authors point out status spongiosus (vacuolated defects of the gray and white brain tissue), which was especially marked at the apex of the convolution; laminar loss of the ganglion cells (in the second and third convolutions), and areas of demyelinization (in the temporal lobe, supramarginal or occipital lobe convolutions). In some cases, the deeper laminae (fifth and sixth) showed swollen, balloon-like cells (in the third cortical layer) as seen in Pick's disease (atrophy of the brain), in addition to other nerve cell changes as described by Nissl. The myelin fibers exhibited marked destruction. Of the catabolic products, iron pigment was found in all the cases. The status spongiosus and the cortical atrophies are regarded as due, not to the paralytic process, but to a combination with a functional disturbance of circulation, as the distribution of the atrophy in these cases followed the branches of the middle cerebral artery.

GEORGE B. HASSIN.

SPONTANEOUS SUBARACHNOID HEMORRHAGE IN RELATION TO CEREBRAL ANEURYSM. I. STRAUSS, J. H. GLOBUS and S. W. GINSBURG, Arch. Neurol. &. Psychiat. **27**:1080, 1932.

By "spontaneous subarachnoid hemorrhage" is meant massive extravasation of blood into the subarachnoid space from spontaneous rupture of a blood vessel. The common anatomic change is arteriosclerosis of the cerebral blood vessels, with or without aneurysm. Inflammatory lesions of blood vessels may also cause aneurysm followed by rupture and hemorrhage. Repeated lumbar puncture to relieve intracranial tension is indicated. Such hemorrhage may occur almost at any age, but is most frequent between the ages of 25 and 40 years.

GEORGE B. HASSIN.

BRAIN CHANGES IN MALIGNANT ENDOCARDITIS. I. B. DIAMOND, Arch. Neurol. & Psychiat. **27**:1175, 1932.

The lesions of the brain in thirteen cases of endocarditis were studied. The changes are circumscribed or diffuse, inflammatory or degenerative, usually multiple, and are classified by Diamond as nodules, abscesses, vascular lesions, degenerative lesions and attempts at repair. The nodular structure varies. It may be glial, glial-mesodermal, mesodermal or perivascular, glial-leukocytic, or exclusively leukocytic (miliary abscesses), or may show giant cells. Degenerative lesions with softening and necrosis may result from vascular disturbances. In a state of repair, the nodules are rich in capillaries, many newly formed and scattered among glia and microglia cells. The diffuse changes in the brain combined with those in the meninges make a picture of meningo-encephalitis. Both focal and diffuse lesions of the brain are to be looked on as manifestations of the defense reaction against infection and intoxication. GEORGE B. HASSIN.

ENCEPHALITIS IN MEASLES. A. FERRARO and I. H. SCHEFFER, Arch. Neurol. & Psychiat. **27**:1209, 1932.

Ferraro and Scheffer studied two additional cases of encephalitis in measles. Perivascular, or rather extra-adventitial, proliferation of microglia and demyelinization in the same areas are common features. The axons may also be involved. Microglial changes are less characteristic. The ganglion cells may show changes from simple swelling to complete degeneration. In general, the changes are similar to those in postvaccinial encephalitis. In the two cases, death occurred within thirty-six hours after the onset of the disease. There were diffuse, parenchymal lesions of the brain with involvement of all the lamina of the cortex, especially those of the frontal lobe. The basal ganglions and Purkinje cells were also involved. Oligodendroglia in both the cortex and the white substance showed diffuse swelling. Microglia were less involved, while the astrocytes showed both progressive and regressive changes. Marked proliferation of microglia and demyelinization were absent. Instead, changes of the gray matter were prominent and resembled those occurring in experimental toxemias, for instance, lead poisoning. The differences from the changes usually described are due, they believe, to the time element, as the course was peracute, and the organism did not have time to develop the usual reactive phenomena. GEORGE B. HASSIN.

STRUCTURAL CHANGES IN THE SKIN IN CHRONIC HEREDITARY EDEMA OF THE EXTREMITIES (MILROY'S DISEASE). J. MCGUIRE and P. ZEEK, J. A. M. A. **98**:870, 1932.

The skin of a boy of 15 years who had typical hereditary edema showed: normal epidermis, increased density in the dermal papillary layer, edema with increase in the collagen fibers in the reticular layer, scattered lymphocytic infiltration especially about the small veins and capillaries of the subpapillary network, increase in the subcutaneous tissue with edema, the fluid in places forming pools, and apparent hypertrophy of the arteriolar media.

HETEROTOPIC BONE FORMATION. H. WURM, Beitr. z. path. Anat. u. z. allg. Path. **85**:401, 1930.

From an investigation of heterotopic bone formation Wurm concludes that those calcific deposits the chemical composition of which is similar to bone ash undergo ossification. Cellular (foreign body giant cells with osteoclastic capabilities) as well as humoral forces resorb implanted calcium masses, and superficial lamellar ossification occurs through the activity of proliferated fibrocytes without any preceding cartilaginous stage. In addition, he recognized as a further prerequisite locally increased concentration of calcium ion, which he regards as the factor in the ossification of tendon and muscle following injury rather than displacement of osteoplastic tissue. W. S. BOIKAN.

THE ANATOMIC DIAGNOSIS OF ALCOHOLOGENIC DISEASES OF THE BRAIN. K. NEUBÜRGER, Verhandl. d. deutsch. path. Gesellsch. **26**:395, 1931.

The anatomic diagnosis of the effects of chronic alcoholism on the brain can be easily made in many instances by examination of the corpora mamillaria. Often there are characteristic macroscopic changes, namely, small brown discolorations and softenings of these structures. Microscopic study reveals almost always endarteritis of the small blood vessels, proliferation of the microglia and fatty degeneration of the glia cells, changes that do not appear to occur in other diseases.

C. ALEXANDER HELLWIG.

HISTOLOGIC FINDINGS IN SKELETAL MUSCLES FOLLOWING ELECTRIC SHOCK. S. T. GELLINEK, Wien. klin. Wchnschr. **45**:37, 1932.

Gellinek reports changes in muscles in two instances of sudden death as a result of electric shock. In the first case, a young man died after having come in contact with an alternating current of 380 volts. The individual muscle fibers close to the region where the electric current had entered the body contained distinct spirals, due to a peculiar arrangement of the sarcoplasm. The threads of the spirals appeared thick and dark without showing any recognizable detail; they were clearly noticeable in preparations stained with hematoxylin and eosin, but became more prominent when Heidenhain's technic was applied. They were regular, and the pitches were found at even intervals. The sarcoplasm between the threads of the spirals (constituting the pitches) showed the cross-striations clearly. The diameters of the muscle fibers in the region of the threads were enlarged as compared with the diameters of the pitches or with those of unchanged muscle fibers. The thickness of the threads measured from 13 to 19 microns. Similar changes were noted in the muscles in the second case. The patient had died suddenly after having been in contact with 5,000 volts of alternating current. In this instance, however, a distinct transverse striation was noted in the threads of the spiral. The myocardium was also examined, and similar spirals were found within the muscle fibers. These spirals were not so sharply outlined as the ones in the skeletal muscles, but the regularity of the threads was clearly noted. Gellinek was also able to produce such spiral-containing muscles experimentally in guinea-pigs after the application of an alternating current of 220 volts. Special emphasis is laid on the application of an alternating current. By the use of a direct current, spirals could not be produced. Gellinek notes that the histologic structures of the muscle fibers were apparently, if at all, only slightly altered. The formation of the spirals in the muscles seems a pure electro-energetic effect —according to Gellinek, the first ever noted in the biologic field.

O. SAPHIR.

THE CEREBRAL LESIONS OF DEMENTIA PARALYTICA IN COMPARISON WITH THE LESIONS OF A SPONTANEOUS DISEASE IN CHICKENS. FREDERIC WERTHAM, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:62, 1932.

In investigations of the effects of experimental infection of the chicken's brain with Spirochaeta gallinarum, in which a series of control animals was also examined histologically, a hitherto undescribed disease of chickens was discovered. The main histologic characteristics were: infiltration of the small blood vessels with plasma cells, marked proliferation of the Hortega glia, with formation of typical rod cells, and iron deposits in diffuse distribution in the intra-adventitial spaces of small vessels and, to a much less extent, in the microglia (Hortega cells).

In addition there were: alterations of nerve cells, in diffuse distribution as well as in special regions; small glia cluster, consisting for the most part of microglia, in the white matter and the gray matter of the cerebrum, the cerebellum and the spinal cord: slight infiltration of the meninges with plasma cells, and in some cases marked ependymitis of the ventricles.

The etiology of this spontaneous disease has not been determined. It is unlikely that a spirochete is responsible for the disease. Histoparasitologic examination with appropriate methods revealed no elements that had any similarity to known micro-organisms. Transmission experiments, which are being continued on birds free from this disease, such as canaries, have so far not led to positive results.

The demonstration of these lesions is significant for the following reasons: Iron deposits of the type described have been observed elsewhere only in dementia paralytica (with the exception of very small amounts in three cases of human trypanosomiasis). For this reason, this type of iron deposit was termed "dementia paralytica iron," a designation generally accepted by neuropathologists. The evidence that such iron occurs also in animals opens a way for further investigation of its significance.

The three outstanding histologic signs of this disease of chickens correspond to the three cardinal histologic characteristics of dementia paralytica, namely, plasma cell infiltration of small vessels, "dementia paralytica iron" and the formation of rod cells. The less significant histologic lesions of the spontaneous disease of chickens, such as changes of nerve cells, small glia clusters, ependymitis, etc., also occur in dementia paralytica. It may therefore be concluded that the histologic lesions of dementia paralytica are not specific, but constitute a reaction of the central nervous system that may occur under different circumstances.

It is likely that some of the lesions that have been described as characteristic of infectious and nutritional disorders in birds are in reality the effect of this spontaneous disease, just as the lesions of spontaneous encephalitis of rabbits have been taken for the effect of syphilis or epidemic encephalitis.

FREDERIC WERTHAM.

OCHRONOSIS IN CATTLE. H. FINK and W. HOERBURGER, Ztschr. f. physiol. Chem. **202**:8, 1931.

A case of ochronosis (osteohemochromatosis) in a cow is described. The bones were mahogany brown and showed in filtered ultraviolet rays the characteristic bright red porphyrin fluorescence. The enamel of the teeth, in contrast to the dentin, did not fluoresce. The myeloid and fat marrow did not show fluorescence. Analysis of the bones gave a relatively small amount of uroporphyrinoctamethyl ester. For the identification of this substance the p_H fluorescence curve was used. The ground spongy bones of the pelvis, scapula, etc., gave a definite hemochromogen spectrum, but not a porphyrin spectrum, while the hemochromogen spectrum was absent in the long bones and only an alkaline porphyrin spectrum was present. The iron content of the bones was within normal limits. Urohemin could not be demonstrated.

WILHELM C. HUEPER.

DEATH FROM RUPTURE OF A TUBERCULOUS ANEURYSM OF AN INTERCOSTAL ARTERY. E. LINDHAGEN and E. KARLMARK, Acta med. Scandinav. **76**:88, 1931.

A case of fatal hemothorax from a tuberculous aneurysm of the fourth right intercostal artery in pleural tuberculosis is described. The bleeding took place gradually through a small opening that passed through tuberculous granulation tissue.

SCLEROSIS AND ANEURYSM OF THE PULMONARY ARTERY WITH PATENT FORAMEN OVALE. H. OKKELS and F. THERKELSEN, Acta path. et microbiol. Scandinav. **9**:214, 1932.

A man, 31 years old, had suffered from marked dysemia and cyanosis since childhood. After death there were found pulmonary arterial sclerosis with patent foramen ovale and an aneurysm of the pulmonary artery just above the valves. There was no defect in the septum, and the ductus botalli was closed.

Pathologic Chemistry and Physics

DISTRIBUTION OF SUGAR BETWEEN BLOOD CELLS AND PLASMA. MARTIN JACOBY and HELENE FRIEDEL, Biochem. Ztschr. **244**:356, 1932.

Using the Hagedorn-Jensen method, the authors find that the corpuscular sugar almost never surpasses 30 per cent of the total blood sugar, but is usually far below this. In the presence of increased blood sugar, the corpuscular fraction is relatively decreased, probably on account of a limited sugar capacity of the cells. The corpuscular sugar concentration after the addition of dextrose to the blood is in general smaller at an acid reaction than at a neutral reaction. This is mainly due to an increased volume of the cell at an acid reaction. This increase in volume is due to an increased water content without a corresponding increase of the sugar content of the cell. The volume of the cells has therefore to be considered in the calculation of the cellular sugar fraction.

WILHELM C. HUEPER.

THE IODINE CONTENT OF THE CEREBROSPINAL FLUID. A. HAHN and A. SCHÜRMEYER, Klin. Wchnschr. **11**:421, 1932.

Iodine is a normal constituent of the cerebrospinal fluid. With an iodine value of the blood of about 10.62 per cent, there is a concentration in the spinal fluid of about 7.42 per cent—approximately a 70 per cent relation to the iodine content of the blood. With potassium iodide therapy and a hundred-fold increase of the iodine content of the blood, there is only a sixfold increase in the cerebrospinal fluid and the relation to the content in the blood drops to about 3.3 per cent. The permeability of the meninges for iodine increases with fever, and the relation thereby rises to about 7.5 per cent.

EDWIN F. HIRSCH.

WAVELENGTH OF X-RAYS AND BIOLOGIC EFFECT. CARL HOFFMANN, Strahlentherapie **43**:140, 1932.

Opalina ranarum inoculated into a weakly alkaline culture liquid was exposed to 500 roentgens and 1,000 roentgens and then stained with trypan blue or light green. After a primary state of increased motility following irradiation in the series treated with 500 roentgens, a gradual decrease and ultimate arrest of this activity occurred after three hours. Eight hours later, 50 per cent of the organisms contained dye granules. About 80 per cent of these organisms contained granules of rather coarse character, while the others had very fine granules as seen under normal vital-staining conditions. Exposure to intense light could still elicit movement of the cilia. After eighteen hours, all cells contained coarse dye granules, and some had a diffuse plasmatic stain. The nuclei became pyknotic and intensely stained. The cells were swollen. After two days, some of the organisms showed signs of recovery, but after another twenty-four hours 80 per cent of the opalinae were dead, and the rest showed evidence of degeneration with numerous large stained flakes in the cytoplasm. After ninety-six hours, these organisms had completely recovered and had even increased in number. Attempts to determine the hydrogen ion concentration of the cells with neutral red and methyl red gave inconclusive results. Irradiation with 1,000 roentgens produced similar but more acute changes. After eight hours, 75 per cent of the organisms were dead or fragmented. Irradiation of the culture medium before inoculation was ineffective.

WILHELM C. HUEPER.

Microbiology and Parasitology

RHINOSPORIDIUM SEEBERI IN A NASAL POLYP: THE FOURTH NORTH AMERICAN CASE. G. S. GRAHAM, Am. J. Clin. Path. **2**:73, 1932.

A case is reported of rhinosporidial infection in a nasal polyp. The patient was a 12 year old Negro, born in Georgia, and had resided since the age of 4 in a small

coal-mining village in Alabama. The source of the infection is unknown, no other similar condition having been observed in the community for at least ten years. The case illustrates the remarkable discontinuity of the infection, of which more than forty cases have been reported during the past thirty years from three widely separated localities—India, Argentina and the United States. A preoperative diagnosis should be made without difficulty through recognition of the characteristic spores in the nasal secretions.

AUTHOR'S SUMMARY.

HYMENOLEPIS NANA. T. TSUCHIYA and E. H. ROHLFING, Am. J. Dis. Child. **43**: 865, 1932.

Two cases occurring in children in St. Louis, in addition to the cases previously reported by Goldman, are described. Neither clinical nor laboratory findings were indicative of pathologic conditions in these children. With a view to determining the possible source of the infection, a cross-infection experiment with ova from human sources was carried out in rats. Two of six clean rats were successfully infected. Subsequent experiments showed that five of ten clean rats were infected with the ova of the two rats previously infected with human materials. Since there is the possibility of adapting the human parasites to rats, rats in turn may become one of the sources of the infection in human beings.

AUTHORS' SUMMARY.

ANCYLOSTOMA BRAZILIENSE AND THE ETIOLOGY OF CREEPING ERUPTION. WALTER E. DOVE, Am. J. Hyg. **15**:664, 1932.

An incidental intestinal infection of A. caninum in a boy in Texas is reported. Penetrations of human skin with mixed larvae of A. caninum and Necator americanus cultured from a boy produced swelling and short vesicular lesions during the first three days. Penetrations of the skin of a volunteer by larvae of a boy-to-cat strain of A. braziliense produced lesions of creeping eruption, which were active for more than thirty-five and fifty-four days. Penetrations of the human skin with a boy-to-dog strain of A. caninum produced short linear lesions, which disappeared in less than fourteen days.

AUTHOR'S SUMMARY.

HUMAN AMOEBIC ULCERS. KENTARO HIYEDA and MICHISABURO SUZUKI, Am. J. Hyg. **15**:809, 1932.

When amebas enter the lumen of the large intestine, the intestinal epithelium produces an enormous amount of mucus, which prevents many of the amebas from entering the tissues. The struggle between them and the mucus may last for from two to eight days; this may be verified experimentally. If the amebas succeed in coming in contact with the epithelium, they give rise to necrosis or necrobiosis of the superficial epithelial layer. They multiply when they come in direct contact with the tissue, even though they are actually in the lumen of the intestine. Toxic substances produced by them lead to necrosis of the mucous membrane. In this way, the roughness of erosion of the superficial mucous membrane occurs. The amebas make their way deeper into the intestinal wall, multiply there and produce a large area of necrosis; finally a typical large crater ulcer develops. If the secondary bacterial infection is severe, there results an abscess. A crater ulcer may also result from the bursting of such an abscess, although this is not usual. The amebas within the tissue of the submucosa make their way mostly longitudinally to the axis of the intestine. This is why the ulcers are wider below the surface, and why they build the tunnel-like communications under the intact epithelial covering. If the regenerating activities of the epithelial cells and other intestinal tissues overcome the invading power of the amebas, the reparation of the ulcer occurs, causing a thickening of submucosa. But *restitutio in integrum* is never reached as long as the amebas are present. If small ulcers occur with only a few amebas in their vicinity, the balance between amebic vitality and tissue

resistance is well kept, and no marked intestinal symptoms may occur. This is the condition of the ameba carrier. Cellular infiltration in amebic ulcers mainly depends on a mixed infection of bacterial origin. None of the leukocytes have a special affinity for the amebas or for their products. The amebas in equilibrium with the local tissues will remain so for long periods, but if the equilibrium is broken, the amebas may become active and give rise to an exacerbation.

FROM AUTHORS' SUMMARY.

INTRANUCLEAR AND CYTOPLASMIC INCLUSIONS ("PROTOZOAN-LIKE BODIES") IN THE SALIVARY GLANDS AND OTHER ORGANS OF INFANTS. S. FARBER and S. B. WOLBACH, Am. J. Path. **8**:123, 1932.

In the submaxillary glands removed in a series of 183 postmortem examinations on infants, large cells containing intranuclear and cytoplasmic inclusion bodies ("protozoan-like bodies") were found in 22 cases (12 per cent). In addition, there are reported the cases of 2 older children with inclusions in the parotid and submaxillary glands, and 2 instances in which inclusions were found in epithelium-lined spaces of the liver, lungs, kidneys, pancreas and thyroid gland, making a total of 26 new cases to be added to the 25 already recorded in the literature. All the patients in this series were less than 17 months of age, the majority being under 1 year. The inclusions are apparently identical with those found in the submaxillary glands of guinea-pigs, and are generally similar to inclusions found in diseases due to filtrable viruses. Clinical and pathologic studies revealed no association with any distinctive feature or group of symptoms or morbid changes. The frequency of the observation in our postmortem examinations suggests geographic factors affecting occurrence and leads naturally to a suspicion of the existence of an infantile disease caused by a filtrable virus. If there is such a disease, there are no distinctive clinical or pathologic features permitting its recognition in the wards or in the pathologic laboratory. The clinical and pathologic findings in the "positive" instances resemble, in general, those in the entire group studied.

AUTHORS' SUMMARY.

YELLOW FEVER ENCEPHALITIS OF THE MONKEY. E. W. GOODPASTURE, Am. J. Path. **8**:137, 1932.

A histologic and cytologic study has been made of an encephalitis of monkeys (Macacus rhesus) inoculated intracerebrally with the mouse strain of the virus of yellow fever. The lesion is an acute, disseminated encephalomyelitis, extending apparently throughout the central nervous system, affecting the cellular tissues and causing necrosis of ganglion cells, both sensory and motor. Intranuclear inclusions sometimes resembling, but more often differing from, those characteristic of yellow fever have been demonstrated in ganglion cells. On immunologic and histologic grounds it is judged that the virus of the mouse and monkey encephalitis represents a biologically modified strain of the virus of yellow fever. Cytologically, the evidence of morphologically characteristic yellow fever intranuclear inclusions in the brains of encephalitic monkeys inoculated with the mouse virus is inconclusive.

AUTHOR'S SUMMARY.

INTRANUCLEAR INCLUSIONS IN MONKEYS UNACCOMPANIED BY SPECIFIC SIGNS OF DISEASE. W. P. COVELL, Am. J. Path. **8**:151, 1932.

From these observations and those of Stewart and Rhoads, it seems likely that monkeys must be listed with man, guinea-pigs, rats, rabbits and dogs as animals in which sometimes lurk one or more viruses capable of producing intranuclear inclusions in the absence of recognizable clinical symptoms. Particularly is this of interest when monkeys are employed for experiments with viruses that in the proper environments are definitely disease-provoking, such as those of poliomyelitis, yellow fever, chickenpox and measles.

AUTHOR'S SUMMARY.

TORULA INFECTION. J. W. WATTS, Am. J. Path. **8**:167, 1932.

Two cases of torula infection are presented. In the first, the infection was generalized, but the symptoms were almost entirely cerebral. A remarkable collection of pathologic changes was present in the brain: diffuse meningitis, granulomas in the meninges, marked endarteritis and proliferation of adventitial elements of the meningeal vessels, an infarct in the pons, areas of softening and focal disappearance of the granular and Purkinje cells in the cerebellum, diffuse changes in ganglion cells, increase of neuroglia, nerve fiber destruction, myelin sheath damage and encephalitis by extension in the striate body. The second case falls into the group which Freeman considers embolic phenomena. Mucicarmin was found to be an excellent differential stain, not only making it easy to identify the organism by its distinctive color, but bringing out details of structure not hitherto recorded. Two strains of yeastlike bodies were isolated: the one producing no pigment falls into the torula group; the one producing pigment appears to be a chromotorula. The organism was nonpathogenic for guinea-pigs, rats and mice. The respiratory tract is probably the portal of entry in most cases. The infarct in the pons, endarteritis of numerous meningeal vessels with the torula in the intima and softenings in the cerebellum in case 1 add weight to the theory that cystic cavities in the deep white and gray matter are embolic phenomena, and that dissemination is by the blood stream.

AUTHOR'S SUMMARY.

CULTIVATION OF B. LEPRAE WITH EXPERIMENTAL LESIONS IN MONKEYS. MALCOLM H. SOULE and EARL B. MCKINLEY, Am. J. Trop. Med. **12**:1, 1932.

The experiments described included (1) the experimental production of granulomatous lesions suggestive of early lesions of leprosy in two species of monkeys by intradermal inoculation of material from human leprosy, (2) the cultivation of acid-fast bacilli (presumably B. leprae) from nodules of human leprosy on several artificial mediums in various gaseous environments, and (3) the experimental production of granulomatous lesions suggestive of early leprosy in two species of monkeys by the intradermal inoculation of cultures of acid-fast bacilli from material from human leprosy, grown on artificial mediums. We believe the experiments indicate a step forward in the fulfilment of Koch's postulates for the causative agent in leprosy.

AUTHORS' SUMMARY.

FAT THERAPY IN EXPERIMENTAL TUBERCULOSIS OF RABBITS. SAMUEL A. LEVINSON, Am. Rev. Tuberc. **23**: 527, 1931.

Feeding egg yolk and cholesterol in oil to rabbits gives rise to a relatively rapid increase of the cholesterol level of the blood. Feeding of cotton-seed oil is not injurious to the mucosa of the gastro-intestinal tract. Animals which were inoculated with tubercle bacilli and which received various fat feedings showed a gain in weight. Animals fed with oil and not inoculated with tubercle bacilli usually lost weight. Overfeeding with cholesterol, leading to oversaturation of the body of the rabbit with cholesterol, does not protect the animals against tuberculosis.

H. J. CORPER.

CALCIFICATION FOLLOWING MASSIVE DOSES OF VIOSTEROL IN EXPERIMENTAL BOVINE TUBERCULOSIS OF GUINEA-PIGS. T. T. WALKER and T. D. SPIES, Am. Rev. Tuberc. **24**:65, 1931.

Administration of repeated massive doses of viosterol to guinea-pigs with acute bovine tuberculosis causes extensive calcification within the caseous lesions. This calcification is much more marked than that which occurs in similar lesions of tuberculosis without the use of viosterol. Calcium is deposited also in apparently normal tissue of the heart, liver and kidneys of the tuberculous animals treated with viosterol.

H. J. CORPER.

THE DISEASE CAUSED BY FILTRATES OF TUBERCLE BACILLUS CULTURES. M. PINNER and M. VOLDRICH, Am. Rev. Tuberc. **24**: 73, 1931.

Filtrable forms of the tubercle bacillus are not demonstrable in pure cultures of the bacillus by the methods tested by Pinner and Voldrich, and they contend that the existence of filtrable forms has not been proved. Filtrates from broth cultures of the tubercle bacillus cause a characteristic disease in guinea-pigs. The nosogenic agent of this disease is not a living virus, because (1) it is not present in whole cultures of the tubercle bacillus grown on solid mediums, (2) it is thermostabile, and (3) it is not transmissible by animal passage. This disease is probably caused by a specific tuberculotoxic substance, which may be identical with tuberculin.

H. J. CORPER.

THE LYSIS OF TUBERCLE BACILLI IN SPUTUM. L. ROSENTHAL and V. B. DOLGOPOL, Am. Rev. Tuberc. **24**:351, 1931.

Tubercle bacilli undergo lytic changes in sputum if the specimen is allowed to stand a few days before examination. A certain degree of lysis may occur at room temperature. At 37 C., the lysis becomes evident after ten days, following an initial increase in the number of the tubercle bacilli. The optimum temperature for the lysis is from 48 to 60 C. The concomitant flora of the sputum does not affect the staining ability of the tubercle bacilli. The lytic agent is probably the product of autolysis of leukocytes.

H. J. CORPER.

AN ATTEMPT TO GROW PARAMECIA IN PURE CULTURES OF TUBERCLE BACILLI. A. P. DAMEROW, Am. Rev. Tuberc. **24**:363, 1931.

Cultures of avirulent human tubercle bacilli will not support growth and reproduction of Paramecium caudatum. Attempts to develop tolerance for tubercle bacilli in paramecia were unsuccessful. Tubercle bacilli are rapidly washed from paramecia after they have been in contact for varying intervals of time up to two weeks, indicating that probably the tubercle bacilli were not taken up by the paramecia.

H. J. CORPER.

THE EFFECT OF IRRADIATED ERGOSTEROL ON CALCIFICATION IN PULMONARY TUBERCULOSIS. J. KAMINSKY and D. L. DAVIDSON, Am. Rev. Tuberc. **24**: 483, 1931.

Oral administration of small doses of viosterol caused augmentation of serum calcium in patients with pulmonary tuberculosis, but such an increase in serum calcium did not influence to any appreciable extent the degree of calcification in pulmonary lesions, so far as this could be demonstrated by roentgenograms.

H. J. CORPER.

EFFECT OF ENVIRONMENT ON NORMAL AND TUBERCULOUS GUINEA-PIGS. MYRTLE GREENFIELD, Am. Rev. Tuberc. **24**:695, 1931.

Normal guinea-pigs live longer in an open building than in either a wooden or a glass building. Guinea-pigs are more able to combat tuberculous infection when housed in an open building than when housed in either a wooden or a glass building. Offspring of tuberculous guinea-pigs housed in an open building are able to live and produce young, while offspring of tuberculous guinea-pigs housed in either a wooden or a glass building live only a short time.

H. J. CORPER.

CHEMICAL AND BIOLOGICAL PROPERTIES OF THE PHOSPHATIDE FROM THE TUBERCLE BACILLUS. C. H. BOISSEVAIN and C. T. RYDER, Am. Rev. Tuberc. **24**:751, 1931.

Intraperitoneal injection into guinea-pigs of a phosphatide (phosphatide A3 of Anderson) causes formation of tuberculous tissue and cutaneous hypersensitiveness.

It is impossible to free this phosphatide from acid-fast bacilli and bacillary débris by centrifugation, precipitation or filtration of its ethereal solution. Filter candles that retain bacilli suspended in water let the same bacilli pass through when suspended in ether. It is possible to free the phosphatide from bacteria and bacterial débris by dialysis of the ethereal solution through a rubber membrane, subsequent solution in a mixture of water, alcohol and ether, and filtration through a Mandler filter candle. Intraperitoneal injection of the purified phosphatide does not cause formation of tuberculous tissue or cutaneous hypersensitiveness. The tissue reaction to phthioic acid is of the nature of a foreign body reaction.

H. J. CORPER.

ACUTE BACTERIAL ENDOCARDITIS DUE TO BACTERIUM ACIDI-LACTICI. LEWIS DICKAR, Arch. Int. Med. **49**:788, 1932.

Two cases of endocarditis caused by B. acidi-lactici, closely resembling cases of infection with B. coli, are reported because of their rarity. More complete bacteriologic studies of cases of sepsis due to B. coli will undoubtedly bring to light more examples of infection with B. acidi-lactici. The coincidence of involvement of the aortic valve in two cases of endocarditis caused by B. acidi-lactici and in two cases caused by B. coli is pointed out.

AUTHOR'S SUMMARY.

EXPERIMENTAL YAWS. T. B. TURNER and J. H. CHAMBERS, Bull. Johns Hopkins Hosp. **50**:253, 1932.

The virus of yaws taken early in the disease from ten native Haitians was transferred to both rabbits and monkeys. Eight strains of yaws spirochetes were recovered by the inoculation of rabbits and were propagated through a second generation of this species. Of five monkeys (Macacus rhesus) inoculated with material from as many different patients, some presented lesions, but Treponema pertenue could not be demonstrated, and there was no assurance, therefore, that the infection had been transmitted to these animals. Rabbits inoculated by three methods—testicular injection, intracutaneous injection and granulating wound—presented definite lesions of yaws only after testicular inoculation. Of thirty-four rabbits inoculated in one or both testes, fourteen presented definite lesions of yaws. A strain of spirochetes of syphilis was successfully transferred from a native Haitian to rabbits. For the transfer of yaws from man to animals, the rabbit proved to be more suitable than the monkey (Macacus rhesus). Only testicular inoculation of the rabbit yielded satisfactory results.

ETIOLOGY OF MULTIPLE SCLEROSIS. A. WEIL, J. A. M. A. **97**:1587, 1931.

Repetition of the experiments of Chevassut and Purves-Stewart failed to produce convincing evidence that, in multiple sclerosis, cultures from spinal fluids yield a filtrable virus and that this virus is responsible for the production of the disease.

The fact that spheres and colonies of spheres may more readily be seen in agar cultures of spinal fluids that have given a positive globulin reaction suggests the precipitation of colloidal protein (or lipid) particles, which become visible in the dark field.

AUTHOR'S SUMMARY.

INFESTATION WITH DIPHYLLOBOTHRIUM LATUM ON THE EASTERN SEABOARD. M. PLOTZ, J. A. M. A. **98**:312, 1932.

Twenty-one cases of infestation with Diphyllobothrium latum are reported from New York City. These are the first from New York State reported in the literature, and include five in which the patients were born in the United States, bringing the total number of reported native cases to thirty-one.

All but two of the patients were females, and all but two Jews.

FROM AUTHOR'S SUMMARY.

Ulcerative Colitis Due to Chronic Infection with Flexner-Y Bacillus. Thomas T. Mackie, J. A. M. A. **98**:1706, 1932.

The Flexner-Y group of dysentery bacilli may cause sporadic cases of mild diarrhea and dysentery. The occurrence of these cases does not require the presence of epidemic conditions. A significant number of the persons concerned may become persistent carriers and may develop ulcerative lesions of the lower part of the bowel, even though the initial acute attack may have been mild. The lesions of chronic bacillary dysentery differ in no respect from those encountered in many of the cases of so-called chronic ulcerative colitis. Intermittence of the excretion of the bacilli is one of the characteristics of chronic infection with the Flexner bacillus, and repeated cultures over a period of weeks may be necessary to demonstrate them. If cultures are taken directly from the floor of the ulcers through the sigmoidoscope, the probability of recovering the organisms is materially increased.

Author's Summary.

The Streptococci of Milk-Borne Septic Sore Throat and Scarlet Fever. A. W. Williams and C. R. Gurley, J. Bact. **23**:241, 1932.

We conclude from our studies on this subject that milk-borne epidemics of septic sore throat and of scarlet fever may be caused, respectively, by one or several agglutinative types of hemolytic streptococci. When scarlet fever predominates, usually the epidemic strain belongs to one of the common scarlet fever agglutinative types; when septic sore throat predominates, the epidemic strain may be one of several agglutinative types, two of which have been demonstrated in these studies and have been called tentatively epidemicus agglutinative type I and epidemicus agglutinative type II.

Authors' Summary.

Specific Enzyme in Cultures of the Bacillus Decomposing the Capsular Polysaccharide of Type III Pneumococcus. R. Dubos, J. Exper. Med. **55**:377, 1932.

An improved method is described for the preparation, concentration and purification of the bacterial enzyme that is capable of decomposing the capsular polysaccharide of the type III pneumococcus. The cultural conditions for the growth of the specific micro-organism must be such that the capsular polysaccharide is completely decomposed before any appreciable amount of free enzyme is released into the medium. This reduces to a minimum the decomposition of the specific substrate by the free enzyme. As a result, a larger part of the specific substance remains as a source of energy for the growing micro-organism, and less enzyme is lost through inactivation during the course of decomposition of the specific substrate. A marked stimulation of growth and of the production of the enzyme occurs when small amounts of yeast extract are added to the medium, and when the cultures are incubated under conditions of increased aeration. Special emphasis is placed on the fact that, thus far, appreciable amounts of the specific enzyme have been obtained only when the capsular polysaccharide itself, or the aldobionic acid derived from it, was present in the culture medium.

Author's Summary.

The Action of a Specific Enzyme upon the Dermal Infection of Rabbits with Type III Pneumococcus. K. Goodner, R. Dubos and O. T. Avery, J. Exper. Med. **55**:393, 1932.

The action of the enzyme that specifically decomposes the capsular polysaccharide of the type III pneumococcus has been tested in dermal infections of rabbits with this pneumococcus. When injected in sufficient amounts, the enzyme is capable of bringing about a favorable and early termination of the experimental disease, which ordinarily is fatal in nearly all instances. The results of the present study yield further evidence that the capsular substance is of great importance

in pneumococcic infection, since, so far as known, the only action of which the specific enzyme is capable is that of decomposing the capsular polysaccharide.

AUTHORS' SUMMARY.

FILTRABILITY OF TUBERCULOUS VIRUS. C. CALLERIO, Ztschr. f. Tuberk. **63**:198, 1932.

Ninni reported that injection of filtrates from cultures of the tubercle bacillus into lymph nodes permitted demonstration of acid-fast elements in the nodes in a high percentage of tests. He made the injections into the tracheobronchial lymph nodes in guinea-pigs. Callerio repeated these experiments, following Ninni's technic in every detail and using even the same strain of tubercle bacilli. Seventy-two guinea-pigs were used, but the results in all cases were negative.

MAX PINNER.

DEMONSTRATION OF SMALL NUMBERS OF TUBERCLE BACILLI. E. DE CARVALHO, Ztschr. f. Tuberk. **63**:305, 1931.

Tubercle bacilli cannot be found microscopically unless from 10,000 to 100,000 are present in 1 cc. of the material. By cultural methods and by inoculation in animals they can be demonstrated when only from 1 to 10 are contained in 1 cc. Using artificial mixtures of negative sputum and a known amount of bacilli, Carvalho found that cultural methods are about as good as inoculation in animals. The treatment of sputum with acids or with alkali will at times prevent small numbers of bacilli from growing on mediums and from producing tuberculosis in guinea-pigs. The most sensitive method for the demonstration of tubercle bacilli is that of the injection of untreated material into guinea-pigs. MAX PINNER.

ROBERT KOCH-HEFT, Ztschr. f. Tuberk. **64**:1, 1932.

This issue is dedicated to commemoration of the fiftieth anniversary of the discovery of the tubercle bacillus by Robert Koch. The single articles deal with certain phases in the development of knowledge of tuberculosis since 1882 and represent reviews rather than original contributions. As such, they are not well suited for abstracting, but since several of them are interesting summaries, a list of the single papers follows:

E. von Romberg: The Significance of the Discovery of the Tubercle Bacillus for Clinical Work.
R. Sauerbruch: Robert Koch.
R. Philip: The Discovery of the Tubercle Bacillus: Some Consequences.
P. Huebschmann: What Did the Discovery of the Tubercle Bacillus Mean for Pathologic Anatomy?
L. Bernard: The Demonstration of Koch's Bacillus in Sputum and the Diagnosis of Pulmonary Tuberculosis.
B. Lange: The Work of Robert Koch and the Newer Research in Experimental Tuberculosis.
A. Calmette: Koch's Bacillus and the Invisible Elements of the Tuberculosis Virus.
E. R. Baldwin: The Cultivation of a Human Tubercle Bacillus During a Period of Forty-One Years.
W. von Drigalski: The Significance of the Discovery of the Tubercle Bacillus for Social Hygiene.
B. Möllers: The Decrease in the Mortality from Tuberculosis During the Last Fifty Years.
O. Roepke: The Diagnostic and Therapeutic Significance of Tuberculin.
E. Küster and W. Strempel: The Standardization of Tuberculin by Intracutaneous Tests in Tuberculous Guinea-Pigs.
E. R. Long: The Chemistry of the Tubercle Bacillus.

B. Bang: The Significance of the Discovery of the Tubercle Bacillus for the Eradication of Tuberculosis in Domesticated Animals.
H. Meissner: The Campaign Against Bovine Tuberculosis.
A. St. Griffith: The Types of Tubercle Bacilli in Lupus.
E. Löwenstein: Remarks About Tubercle Bacillus Bacillemia.

MAX PINNER.

Immunology

THE CRAIG COMPLEMENT-FIXATION TEST FOR AMEBIASIS IN CHRONIC ULCERATIVE COLITIS. EVERETT D. KIEFER, Am. J. M. Sc. **183**:624, 1932.

It is extremely difficult to differentiate between chronic ulcerative colitis and chronic amebic colitis. When the Craig complement-fixation test for infection with Endamoeba histolytica was applied to nineteen patients with chronic ulcerative colitis fifteen gave a strongly positive reaction. No conclusions as to the significance of this are drawn, but it is suggested that chronic ulcerative colitis may be a pyogenic infection superimposed on amebic ulceration. Abstracts of the histories of the nineteen patients are reported. AUTHOR'S SUMMARY.

DESENSITIZATION OF TUBERCULOUS GUINEA PIGS. JOHN WEINZIRL and RUBY M. BOHART, Am. Rev. Tuberc. **23**:393, 1931.

Weinzirl and Bohart made tests to determine the value, for purposes of desensitization, of (*a*) the dialyzed filtrate of a culture of the tubercle bacillus on Long's medium, (*b*) tuberculoproteins derived from the filtrate of the culture on Long's medium, (*c*) tubercle bacilli killed by carbolfuchsin and (*d*) tubercle bacilli killed and treated with ether. Desensitization, as indicated by the intradermal test, is only partially successful, but the reaction is frequently reduced below 4 plus. If, however, the systemic reaction is considered, desensitization seems to be more complete. Desensitization largely eliminates prostration following the administration of tuberculo-antigens. Of the antigens tested, the ether-killed and treated tubercle bacilli seemed to give the most satisfactory results. The size of the dose must vary with the antigen employed. It should be kept sufficiently low to avoid a violent systemic reaction. The doses should be spaced so as to avoid (*a*) coalescing of the doses and (*b*) a return of sensitization. An interval of less than five or more than ten days between doses is undesirable. H. J. CORPER.

COMPLEMENT FIXATION WITH URINE IN TUBERCULOSIS. M. E. PARKER, Am. Rev. Tuberc. **23**:733, 1931.

Four hundred and eighty-three complement-fixation tests for the detection of tuberculosis were made on urines of tuberculous and nontuberculous persons. It was found that the presence of specific antigens or antibodies in the urine, as demonstrated by complement fixation, is highly indicative of a tuberculous lesion somewhere in the body, but not necessarily in the urinary system. A negative result has no diagnostic significance. H. J. CORPER.

THE PHAGOCYTOSIS OF TUBERCLE BACILLI. M. BORQUIST and C. ROWE, Am. Rev. Tuberc. **24**:172, 1931.

Micromanipulation of monocytes and clasmatocytes shows that they differ in consistency, a monocyte being fragile and easily disintegrated, and a clasmatocyte being distinctly more resistant, more sticky and more elastic than a monocyte. These cells with ingested tubercle bacilli were studied (1) on flat preparations both with neutral red and without stain for periods of from two to eleven hours, and (2) on fixed and stained smears of mixtures of cells and bacteria that had been incubated in hanging drops. Monocytes, clasmatocytes and epithelioid cells with ingested bacilli were studied in smears of pulmonary tissue and peritoneal

exudates obtained from tuberculous animals. There is no evidence that ingested tubercle bacilli of bovine strains are fragmented by any of the cells studied. Bacilli inside cells neither took up neutral red stain nor appeared disintegrated. Epithelioid cells contained many more bacilli than other cells, but no greater number of life cycle changes were seen within them. These experiments suggest that the longevity of the epithelioid cell, rather than a multiplication of bacilli within it, may account for its greater content of bacilli as compared with the clasmatocyte.

H. J. CORPER.

EFFECT OF ACID HYDROLYSIS OF THE POLYSACCHARIDE FROM THE HUMAN TUBERCLE BACILLUS. K. L. MCALPINE and P. MASUCCI, Am. Rev. Tuberc. **24**:729, 1931.

The polysaccharide obtained from the filtrate of a culture of the human tubercle bacillus on Long's synthetic medium has been split by mild acid hydrolysis into two fractions: an alcohol-insoluble fraction, containing large amounts of combined mannose and a small amount of free reducing sugars, which is readily obtained in the form of a white, dry powder having a relatively high optical rotation and a low precipitin titer; and an alcohol-soluble fraction, containing most of the arabinose and large amounts of free reducing sugars, which is a bright yellow gum of low optical rotation and relatively high precipitin titer. During acid hydrolysis of the polysaccharide the lowering of the precipitin titer proceeds at a much greater rate than the cleavage of the polysaccharide into the simple sugars.

H. J. CORPER.

POLYSACCHARIDE IN FILTRATES OF CULTURES OF THE TUBERCLE BACILLUS ON LONG'S SYNTHETIC MEDIUM. P. MASUCCI, K. L. MCALPINE and J. T. GLENN, Am. Rev. Tuberc. **24**:737, 1931.

The growth of human and bovine tubercle bacilli on Long's synthetic medium is characterized by the appearance in the medium of substances that form a precipitate with serum prepared against human tubercle bacilli. The filtrate of the bovine culture contains much less of the reacting substance (polysaccharide) than that of the human culture. In the polysaccharide, the active radical appears to be the pentose.

H. J. CORPER.

LYSOZYME AND TUBERCULOSIS. H. J. CORPER, Am. Rev. Tuberc. **25**:59, 1932.

Lysozyme prepared from the liver or the spleen of the dog or the guinea-pig did not have an inhibitory or bactericidal effect on tubercle bacilli in vitro. Its action does not appear to be a factor in organic susceptibility to tuberculosis in these animals. The experiments reported also make it appear unlikely that lysozyme plays a significant part in susceptibility or resistance to tuberculosis in man.

H. J. CORPER.

SEROLOGICAL REACTIONS WITH HEMOLYTIC STREPTOCOCCI IN ACUTE BACTERIAL INFECTIONS. W. S. TILLETT and T. J. ABERNETHY, Bull. Johns Hopkins Hosp. **50**:270, 1932.

Serums from patients acutely ill with a variety of bacterial infections are capable of agglutinating certain strains of hemolytic streptococci. This capacity is demonstrable early after the onset of the illness, persists during the active stage, and disappears soon after recovery. Four strains of S. hemolyticus, derived from different diseases, are agglutinable. Agglutinability is destroyed by heating cultures to the thermal death point. Agglutinable cultures killed with formaldehyde are not altered. The protein fraction of serum precipitated by carbon dioxide, under the conditions described, contains the constituent reactive with streptococci. By this method, serums from patients with typhoid fever were fractionated, and the

agglutinins for typhoid bacilli and hemolytic streptococci were separated. The implications of the parallelism of altered suspension stability of red blood cells and streptococcic agglutination are discussed. AUTHORS' SUMMARY.

CARBOHYDRATES ADSORBED ON COLLOIDS AS ANTIGENS. J. ZOZAYA, J. Exper. Med. **55**:325, 1932.

Evidence is given that polysaccharides can be rendered antigenic by haptogenic adsorption on a colloid carrier. The polysaccharides studied were those of Bacillus anthracis, Meningococcus, Streptococcus viridans (Bargen), Bacillus proteus, Bacillus morgani, Bacillus dysenteriae, both the Shiga and the Hiss type, and Pneumococcus. With the polysaccharide of type III pneumococci, I have been unable in six weeks to produce any detectable protective antibodies, but was able to produce anticarbohydrate antibodies. All the bacterial carbohydrates were nonantigenic alone when used in the doses indicated, though containing some nitrogen. Dextran, which was free from nitrogen, was also rendered antigenic by the adsorption method. AUTHOR'S SUMMARY.

IMMUNOLOGICAL REACTIONS BETWEEN DEXTRAN POLYSACCHARIDE AND SOME BACTERIAL ANTISERA. J. ZOZAYA, J. Exper. Med. **55**:353, 1932.

Dextran, the synthetic polysaccharide produced by Leuconostoc mesenterioides from saccharose, reacts immunologically with antipneumococcus serums and with serums prepared against some of the Salmonella and some of the types of Streptococcus viridans (Bargen). This immunologic relationship is independent of the specific antipolysaccharide antibodies of these serums, suggesting the existence of a distinct antibody produced by an active group of the specific bacterial polysaccharide, which is similar to or identical with the active group of the dextran polysaccharide. AUTHOR'S SUMMARY.

THE MECHANISM OF PNEUMOCOCCUS IMMUNITY. H. K. WARD, J. Exper. Med. **55**:511 and 519, 1932.

Type III antipneumococcus serum, after absorption with the specific carbohydrate, no longer forms a precipitate with the carbohydrate, but still has a definite, although diminished, bactericidal action on virulent pneumococci. Such an absorbed antiserum still retains some of its power to neutralize the antibactericidal effect of the specific carbohydrate in a bactericidal test, showing that absorption with the carbohydrate does not remove all the anticarbohydrate antibody from an antiserum. This carbohydrate neutralization test is a much more delicate method for detecting the anticarbohydrate antibody (precipitin) than the precipitin test. There is, therefore, no necessity to predicate another antibody to explain the bactericidal action of a carbohydrate-absorbed antiserum or a similar result in a mouse protection test. The specific carbohydrate has a definite antibactericidal action, but it is demonstrated that, were it present in this form in the body during pneumonia, it could not conceivably be produced in sufficient quantity to influence the disease.

There is in the filtrate of a five day broth culture of type III pneumococcus a type-specific substance which has a very powerful antibactericidal action. If the precipitinogen content of the broth filtrate and the specific carbohydrate are taken as the basis of comparison, it requires approximately one thousand times as much antiserum to neutralize the broth filtrate as is necessary to neutralize the specific carbohydrate. The active substance in the broth filtrate appears to be related to the specific carbohydrate. Its possible nature is discussed. A similar substance, but in stronger concentration, was found in the filtrate of a lung obtained at autopsy in a case of type III pneumonia. The influence of this substance on the disease is discussed. One specimen of type III convalescent blood, though comparatively weak in anticarbohydrate antibody (precipitin) was better

able to neutralize the broth filtrate and the lung filtrate than a corresponding mixture of normal blood and antiserum. Two specimens of type II convalescent blood neutralized the type III broth filtrate efficiently.

AUTHOR'S SUMMARIES.

THE RÔLE OF CONDITIONAL REFLEXES IN IMMUNITY. J. METALNIKOW, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**:338, 1932.

This article is a criticism of the results published by E. Friedberger and I. Gurwitz (*Ztschr. f. Immunitätsforsch. u. exper. Therap.* **72**:173, 1931; abstr., ARCH. PATH. **13**:518, 1932)—results that entirely contradicted those originally published by Metalnikow (*Ann. Inst. Pasteur.* **46**:131, 1931; abstr., ARCH. PATH. **12**:496, 1931). Friedberger and Gurwitz did not adhere to the principles as laid down by Pavlov and his school for experimental work on conditional reflexes. Their method of evaluating results carried with it a serious source of error. Metalnikow believes that this fully explains the contradictory results.

I. DAVIDSOHN.

ADSORPTION OF THE ANTIGENIC FRACTION FROM ALCOHOLIC ORGAN EXTRACTS, FROM LECITHIN AND CHOLESTEROL. A. J. WEIL and J. BERENDES, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**:341, 1932.

The adsorption and subsequent separation from the adsorbent was accomplished with kaolin. Alcoholic tissue extracts of heterophilic and nonheterophilic organs were used. The antigenic fractions of cholesterol, dihydrocholesterol and di-stearyl-lecithin were adsorbed in a similar manner, but subsequent separation from kaolin was not possible.

I. DAVIDSOHN.

THE SO-CALLED FRACTIONS OF THE COMPLEMENT. KARL DEISSLER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**:365, 1932.

The so-called fourth fraction of the complement is the one that is destroyed by the action of ammonia and ammonium salts; the third fraction is destroyed by yeast and cobra poison. The two fractions complement each other. The "Mittelstück" and "Endstück" are not affected by the action of the aforementioned substances. The fourth fraction acts directly on the sensitized antigen, which is contrary to the behavior of the third fraction. In the complement fixation the fourth fraction is used up.

I. DAVIDSOHN.

IMMUNIZATION WITH LECITHIN FROM HUMAN BRAIN. F. PLAUT and H. RUDY, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**:385, 1932.

There was no specific antigenic response in rabbits immunized with a mixture of hog serum and a purified lecithin product, prepared by Plaut and Rudy from human brain. Addition of pure cholesterol to the hog serum-lecithin mixture did not change the result. The antigenic response obtained with the commercial preparations of lecithin is probably due to admixtures, possibly the so-called egg yolk antigen. The results are a confirmation of the report of Levene, Landsteiner and Van Der Scheer (*J. Exper. Med.* **46**:197, 1927).

I. DAVIDSOHN.

THE RELATION OF THE BLOOD ANTIGENS IN BACILLUS PARATYPHOSUS B AND BACILLUS DYSENTERIAE SHIGA TO CERTAIN ANIMAL CELLS AND TO HUMAN RED BLOOD CELLS. M. EISLER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**:392, 1932.

B. paratyphosus B produces in rabbits a serum that agglutinates specifically but does not lake human blood A, and agglutinates as well as lakes sheep blood. These antibodies react with a suspension of B. paratyphosus B and with the aqueous and alcoholic extracts of this organism, but not with the carbohydrate

fraction. They react also with the alcoholic extracts of sheep blood and guinea-pig kidney. Pure alcohol inhibited the lysis of sheep blood as well as did alcoholic extracts of B. paratyphosus B. Human A blood and peptone Witte fix the anti-A agglutinins. B. paratyphosus B has only a limited binding capacity. The two types of antibodies in the immune serum are of the Forssman type and are produced by fractions of the Forssman antigen in the bacteria. The complete Forssman antigen is present in the tissues of the guinea-pig. The two partial Forssman antigens in B. paratyphosus B are not identical, the human A-fraction being water-soluble and nonalcohol-soluble, while the sheep fraction is identical with the portion of the Forssman antigen present in all human red blood cells. B. dysenteriae Shiga produces in the goat an agglutinin for human blood of all types, but no lysin; in the rabbit it produces agglutinins and lysins for sheep blood but none for human blood. The carbohydrate fraction contains both antigens (the human and the sheep). The sheep antibodies in the immune serums are of the Forssman type and are bound by guinea-pig organs and by the bacteria and their carbohydrate fraction, but not by their alcoholic extracts. The Forssman fraction in B. dysenteriae Shiga is not identical with the one in human blood. The antihuman agglutinin produced in the goat is heterophilic, but not of the Forssman variety. The two blood antigens are not present in all strains of B. dysenteriae Shiga. Immune serums produced by strains possessing these antigenic fractions are specific for such strains and do not react with strains lacking the same antigenic qualities.

I. DAVIDSOHN.

SEROLOGIC DIFFERENTIATION BETWEEN THE ANTERIOR AND THE POSTERIOR LOBE OF THE HYPOPHYSIS. E. WITEBSKY and H. O. BEHRENS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **73**:415, 1932.

Organ-specific antiserums were produced for the posterior but not for the anterior lobe of the hypophysis. They reacted frequently, though not constantly, with brain antiserums and were not species-specific. A very distinct serologic differentiation was obtained between the posterior lobe of the hypophysis and the spinal cord.

I. DAVIDSOHN.

SERODIAGNOSIS OF TUBERCULOSIS. F. KLOPSTOCK, Ztschr. f. Tuberk. **63**:81, 1931.

In systematic studies it was found that the most suitable antigen for complement fixation in tuberculosis is the alcohol-soluble fraction of tubercle bacilli the wax of which has been removed. The action of this antigen can be enhanced by the addition of some of the wax. A positive complement fixation does not necessarily signify active tuberculosis.

MAX PINNER.

EXPERIMENTS WITH PULMONARY LIPASES. D. KANOCZ, Ztschr. f. Tuberk. **63**:113, 1931.

From normal human lungs a lipase can be isolated according to a process developed by Willstätter-Waldschmidt-Leitz. Tubercle bacilli exposed to this lipase lose their lipoids and are transformed into granules. Such granules immunize guinea-pigs effectively against a massive infection with tubercle bacilli. The lipase is bacteriostatic in vitro.

MAX PINNER.

Tumors

THE NATURE AND ETIOLOGY OF CANCER. H. GIDEON WELLS, Am. J. Cancer (supp.) **15**:1919, 1931.

Wells emphasizes that cancer is not an exclusively human affliction. The idea that cancer is especially common in man is correct, simply because man is one of

the few species of animals that is commonly permitted to reach old age. The study of the disease has served to remove all doubts that cancers in animals and man represent fundamentally the same disease. The differences observed depend either on anatomic peculiarities of different species or on other differences between species, for the frequency of each type of cancer varies with each species. In recent cancer research the trend of results is in support of the view that cancer is usually the result of protracted stimulation of tissue growth by nonspecific agents, acting on tissues the susceptibility of which is determined by their hereditary background. With regard to hereditary influence on susceptibility and resistance to cancer, Wells is of the opinion that the existence of this factor is established both for man and animals.

Is cancer increasing in frequency? Wells says, "If I were to take of the statistics the only ones that seem to me, as a pathologist, likely to be reasonably accurate, namely, the data on external or accessible cancer, corrected for age and sex, I should have to conclude that in all probability cancer is increasing to just about the extent that people are kept from dying of something else." The statement that cancer is rare among "uncivilized" races rests on the "most worthless of evidence."

A scholarly review of the subject, it is condensed to about fifty pages, and is here only partly abstracted.

B. M. FRIED.

THE HISTOGENESIS OF THE SO-CALLED "BASAL-CELL CARCINOMA." SAMUEL R. HAYTHORN, Am. J. Cancer (supp.) **15**:1969, 1931.

Of 412 tumors from hair-bearing areas studied for their relationship to hair follicles, 144 were of noncornifying basal cell type. The conception of Krompecher, who traced the genesis of these neoplasms to the basal cells, is denied by Haythorn, who produces evidence that they originate from the hair matrix. Thus evidence of imperfect hair shafts was found in a majority of the new growths. Pigment was present in a few of the tumors, suggesting the distribution of the pigment in the hairs. A heavy basement membrane resembling the vitreous membrane of the hairs was constantly conspicuous about the nests of tumor cells.

On the basis of histologic studies, Haythorn affirms that the tumors should not be called "basal cell" but "hair matrix" cancers. The article is accompanied by thirty-eight good photomicrographs.

B. M. FRIED.

LEUKOPLAKIA OF THE ESOPHAGUS. GEORGE S. SHARP, Am. J. Cancer (supp.) **15**:2029, 1931.

Sharp affirms that leukoplakia of the esophagus is common. He is of the opinion that it is frequently associated with esophageal carcinoma.

B. M. FRIED.

CANCER OF THE THYROID: ITS RADIOSENSITIVITY. CUSHMAN D. HAAGENSEN, Am. J. Cancer (supp.) **15**:2063, 1931.

Haagensen has grouped cancers of the thyroid gland into five distinct groups —each group having a characteristic natural history and a typical structure. Thirty cancers so classified were studied from the point of view of their reaction to irradiation, such as primary regression and definite cure. The data indicated a moderate radiosensitivity of the less anaplastic types of cancer of the thyroid gland, most marked in the adenocarcinoma group. The most rapidly growing and anaplastic types appeared to be uniformly radioresistant. This finding is not in agreement with hitherto proposed laws of radiosensitivity. In determining the type of treatment, Haagensen emphasizes the histologic type of the tumor, its size and its extent.

B. M. FRIED.

TUMORS OF THE THYMUS. HARRY M. MARGOLIS, Am. J. Cancer (supp.) **15**:2106, 1931.

Tumors of the thymus gland may originate from the parenchyma (the cells of the reticulum, the small thymic cells or thymic lymphocytes, and the corpuscles of Hassall) and from the stroma (lymphosarcomas, fibrosarcomas, myosarcomas or lipomas); since the histogenesis of the thymic elements is still *sub judice*, the classification of thymic neoplasms is not possible at present. Margolis considers that the term thymoma for all tumors derived from the parenchyma of the organ is more acceptable than their discrimination into carcinomas and lymphosarcomas.

Tumors included in the group of lymphosarcomas are probably not other than a morphologic variation of a type cell derived from the thymic reticulum. The designation sarcoma should be reserved for tumors derived from elements of the stroma.

The observation of typical corpuscles of Hassall resulting from degeneration of epithelial cells of tumors apparently derived from the thymic reticulum suggests an analogous mode of formation of these thymic corpuscles in the normal thymus. The article is accompanied by very good photomicrographs and by a complete bibliography.

B. M. FRIED.

PRIMARY MELANOCARCINOMA OF THE GALL BLADDER. SOL ROY ROSENTHAL, Am. J. Cancer (supp.) **15**:2288, 1931.

A case of primary melanocarcinoma of the gallbladder with multiple metastases is reported. By studying the various metastatic nodules, it was found that the melanin was present in the cytoplasm in the early stages as a dust-like, light brown pigment. The latter was usually associated with death of the cell and liberation of the melanin, which was in turn found in the cytoplasm of elongated, mobile cells as pigment granules of various sizes, ranging in color from dark brown to black.

B. M. FRIED.

HEMANGIO-ENDOTHELIOMA OF THE THYROID GLAND. CARL O. RICE, Am. J. Cancer (supp.) **15**:2301, 1931.

Rice reports a case of hemangio-endothelioma of the thyroid gland in a woman of 50, which, he states, is the first to be described in the American literature. The tumor does not vary histologically from tumors of the same type found elsewhere in the body. Roentgen therapy, he believes, may prove of value in the treatment.

B. M. FRIED.

PRIMARY PULMONARY SARCOMA. HOWARD A. BALL, Am. J. Cancer (supp.) **15**:2319, 1931.

Ball discriminates between two types of primary pulmonary sarcoma: (1) pulmonary fibrosarcoma with greater or less differentiation, occurring in adults and having a slowly progressive course and (2) pulmonary round cell sarcoma, occurring in young subjects and exhibiting a more rapid course. The latter probably originates from the mesenchymal cells lining the air sacs. He reports a case of the first variety, which occurs with greater frequency. A review of the literature on the occurrence of the disease since 1900 is given. The article is well illustrated and is accompanied by a detailed bibliography.

B. M. FRIED.

SUPRARENAL NEUROCYTOMA WITH METASTASES. M. G. PETERMAN, Am. J. Dis. Child. **43**:655, 1932.

The tumor reported arose from the left suprarenal gland in a boy, aged 3. There was a retroperitoneal mass on the left, which was dark red, weighed 500 Gm., and contained areas of cystic degeneration. The kidney could easily be separated from the mass. The suprarenal cortex was found intact, the tumor replacing the medulla. One metastasis was found in the sacrum, another in the

petrous portion of the temporal bone and a third in the left hemisphere of the cerebellum. The tumor revealed a variegated architecture, but mostly an infiltration of small, round, sarcoma-like cells, and the diagnosis was neurocytoma. The metastases showed the same picture.

PAUL MERRELL.

FORMALDEHYDE TREATMENT OF A TRANSPLANTABLE RAT CARCINOMA. RAYMOND E. GARDNER and ROSCOE R. HYDE, Am. J. Hyg. **15**:509, 1932.

One per cent formaldehyde in physiologic solution of sodium chloride when injected directly into and around Walker rat carcinoma no. 256 produced, after prolonged treatment, complete regressions in a low percentage, but evoked no immunity as tested by reimplantation. Restriction may be attained with certain tumors, but does not seem promising even for experimental investigation. Fresh whole chicken blood and chicken egg albumin, distinctly different proteins antigenically, do not produce inhibitory effects when injected directly into and around a progressive Walker rat carcinoma no. 256.

AUTHORS' SUMMARY.

PRIMARY ANGIOFIBROMA OF THE DIAPHRAGM. E. BURVILL-HOLMES and WILLIAM BRODY, Am. J. M. Sc. **183**:679, 1932.

A case of primary angiofibroma of the diaphragm is reported. The tumor lay between the leaflets of the right dome of the diaphragm. It was composed principally of fibrous tissue, which contained many angiomatous areas, some of capillary and some of cavernous type. The patient died of pulmonary tuberculosis, the presence of the tumor not being suspected. The case is of interest because of the rarity of primary tumors of the diaphragm, less than a score of which have been reported.

SANDER COHEN.

CANCER IN THE ANAMITE. J. BABLET, Hyg. soc. **60**:1014, 1931.

A careful study of statistics in the important centers in Indo-China resulted in certain conclusions. The Anamese in Cochin-China as in Tonkin appear as susceptible to cancer as inhabitants of temperate countries.

Certain localizations have an abnormal frequency in Indo-China. Carcinoma of the penis and neoplasms of the cervix and mouth are frequent in the Anamese, while cancers of the digestive organs are rarely observed. Histologically, the only interesting point is the elevation in the proportion of tumors of the conjunctiva — one sarcoma to six epitheliomas in place of one to twenty in temperate climates.

The susceptibility of the two sexes does not appear to be different. The cancer age is notably lowered in the Anamese.

These conclusions, which represent a step forward in the knowledge of cancer in Indo-China, will undoubtedly be modified with further organization of cancer centers.

H. S. THATCHER.

PERITHELIAL ENDOTHELIOMA OF THE BULBI PILORUM. H. HAMDI, Ztschr. f. Krebsforsch. **32**:377, 1930.

This is a short report of a case of sarcoma of the axilla with cell nests which reproduced with some faithfulness the histologic features of hair follicles, and which the writer terms a perithelial endothelioma of the hair follicles.

EGGERS, Omaha.

EXPERIMENTAL RESEARCHES ON PRECANCEROUS CHANGES IN THE SKIN AND SKIN CANCER. GUSTAV GULDBERG, Acta path. et microbiol. Scandinav., supp. 8, 1931, p. 223.

The object has been to follow in rabbits and mice the local effects of tar on the skin and its various elements, especially the nerves and vessels, from the first

up to the cancer stage. In mice, the effect of tar is found to last longest on the portion between the shoulder blades. Tar of high distillation fractions produces more distinct dermatitis than the lower fractions and than ordinary gas-works tar, but at the same time it is more toxic. The first phase, the reversible, is the period until malignancy appears, and the cutaneous changes in this period may disappear, if the painting is discontinued. But if malignancy has arisen, the process has passed over to the irreversible phase, with subsequent atypical and infiltrating growth of cells. The maximum of tar irritation does not coincide with the maximum of carcinogenic effect. Sometimes there is only atrophy of the skin after previous pronounced symptoms of inflammation. A general tar poisoning with reduction of the power of resistance is not necessary for the development of papilloma and cancer on the painted area. As early as in the first week, epidermal changes with increasing hyperplasia and hyperkeratosis appear. Most of the hairs become atrophied, but some of the root sheaths become the seat of hyperplasia and cyst formation. Papilloma may develop from the hair follicles or from connective tissue proliferation. The carcinoma forms macroscopically two main types, the papillomatous and the ulcus rodens. There are no grounds for regarding incipient carcinoma as a specific form (carcinoid). The carcinoma presents an extreme differentiation of cells and we can distinguish between differentiated and undifferentiated types of cells. In several tar carcinomas, spindle cells were found in varying proportions, and in some of the carcinomas we could follow the transition from squamous epithelium to spindle cells. Some of the tumors were purely spindle-celled. That the cells in such growths are morphologically altered epithelium is possible, but has not been proved. It is also, however, possible that the tumors are pure sarcomas. Pure polymorphous-celled sarcoma has been obtained in the skin of one rabbit after painting with tar. In the corium during the first month of painting there is inflammation of varying intensity. The cell forms vary: in the first two weeks chiefly leukocytes, afterward chiefly lymphocytes, while at the end of the first and in the second month of painting the fibroblasts and fibrillary elements of the corium increase, and at the same time immigration of mast cells occurs in mice, but not in rabbits. Besides the increase in connective tissue there is often a much less pronounced hyperplasia of the elastic tissue. Any absolute parallelism between the increase and the decrease in the elastic tissue and the formation of cancer was not observed. In experiments on mice with heated tar (55 C.) and with tar of high distillation fractions (from 300 to 400 C.), the local inflammatory reaction lasts longer than when gas-works tar of ordinary temperature is used (from 35 to 37 C.). Besides the hyperemia in the painted area there can also be observed in vitally stained preparations a distinct reflex hyperemia. In the nerves of the skin there arises, on painting with tar, both in mice and rabbits, an acute degeneration in the precancerous stage. This degeneration sets in during the first two weeks of painting and is pronounced at the beginning of the second month. Resection of the peripheral nerves leads to a somewhat earlier development of papilloma in the skin on the side on which operation was done than on the control side, but no earlier formation of cancer. Extirpation of the superior sympathetic cervical ganglion together with the adjoining parts of the nervus sympathicus leads to an earlier development of papilloma and cancer in the skin on the side on which operation was done than on the control side. The neuroparalytic hyperemia with increased supply of blood and increased transudation probably constitutes a contributory factor to the earlier occurrence of epithelial hyperplasia and cancer. The nerves therefore have a certain significance in the development of epithelial hyperplasia and growths in the skin. Mainly on the basis of the experiments in resection of nerves in the ears of rabbits, the author adopts the view that vascular changes play an essential rôle in the epithelial hyperplasia and formation of papilloma, but as to what part they play in the development of the cancer itself no definite conclusions can be drawn. In the author's opinion, the cancerization of the epithelial cells is due to an alteration of environment, probably caused by circulatory disturbances and processes arising therefrom. The changes in both the corium and the epidermis must be conceived

as the result of a toxic action of the tar. The toxic substance in the tar must be supposed to act directly on the various elements of the corium, especially on nerves and blood vessels. The long-continued application of tar leads to alterations in the functions not merely of one single kind of tissue but of all the tissue elements.

FROM AUTHOR'S SUMMARY.

Medicolegal Pathology

IMPORTANCE OF HISTOLOGIC EXAMINATIONS OF LUNGS IN LEGAL MEDICINE. A. FOERSTER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:507, 1932.

The hydrostatic test of live birth has no practical value in cases of advanced putrefaction, since it leads to erroneous interpretations. Microscopic examination of the lungs with hematoxylin-eosin alone is not sufficient to decide positively if the distention of the alveoli occurred on account of penetration of amniotic fluid or if it was due to an intravital inflation with air. Weigert's elastic stain, however, allows a quite reliable conclusion, since in instances of respiration the elastic fibers of the alveoli appear tense and stretched, presenting a round or semicircular arrangement, while in cases of aspiration of fluids the elastic fibers are wavelike in appearance. Cadaveric formation of gas is found mainly in the interstitial tissue of the fetal lung, often in the close vicinity of the blood vessels, and the gas bubbles are never surrounded by elastic fibers.

E. L. MILOSLAVICH.

TRAUMA AND RUPTURE OF THE AORTA. ERNST HAMMER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:541, 1932.

A young, healthy sportsman, 25 years of age, suffered suddenly a spontaneous rupture of the ascending aorta, 2 cm. above the aortic leaflets, causing death within eighteen hours. Another healed tear and an old intramural hematoma were found in the aortic arch. Microscopic examination of the aorta in the region of the recent laceration showed many peculiar defects within the elastic apparatus of the media; the elastic fibers appeared torn and pulled apart, but there was no evidence of inflammatory or necrotic processes. The changes are interpreted as traumatic and mechanical. Four types of this peculiar, primary disorder of the median layer of the aorta occur, characterized by absence of concomitant tissue reactions and by a patchy or focal character: (1) necrosis of the media, as described by Wiesel, Stoerk and Epstein, in instances of acute infectious diseases; (2) idiopathic necrosis of the media, type Gsell-Erdheim, due to toxic, infectious injuries or probably avitaminic in origin; (3) disseminated necrosis of the media, type Cellina, apparently the result of senile process, and (4) traumatic elasticorrhexis of the media, type Hammer.

E. L. MILOSLAVICH.

MURDER BY DROWNING. G. BUHTZ, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:557, 1932.

Buhtz briefly reviews the reports of twenty-three cases of murder by drowning and describes four additional criminal drownings of young pregnant women. The analysis of all the twenty-seven cases showed a great prevalence of murdered women, the criminal act being committed by the fiancé in eleven instances, by the husband in three and by the seducing employer in one. Pregnancy was the motive in nine instances. In fourteen of the twenty-seven cases, a serious struggle preceded the violent death, as evidenced by severe bruises and signs of strangulation. In eleven instances, however, there was no evidence of any injuries; in cases similar to these, if careful and exhaustive investigations are not conducted, a suicide is summarily assumed, and a violent or criminal drowning is then readily overlooked.

E. L. MILOSLAVICH.

MICROBIOLOGIC INVESTIGATIONS IN LEGAL MEDICINE. R. E. PERL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:570, 1932.

The murdered body of a young man was found in a pool of muddy water in the close vicinity of a river, and the question arose whether the death occurred in that particular place, or whether the dead body was brought there later on. Autopsy disclosed death by drowning. Detailed bacteriologic and microscopic analysis of various samples of the water in the pool and of the lungs was made. The microscopic examinations were conclusive, since the same kind of protozoans, algae, etc., were detected in the mud as in the fluid from the lungs. The arrested suspect confessed to murder where the body was found.

E. L. MILOSLAVICH.

INTRACRANIAL ANEURYSM IN A SIX YEAR OLD GIRL. K. K. ORTMANN, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:604, 1932.

The autopsy of a 6 year old girl, who died suddenly, disclosed a ruptured aneurysm, the size of a pea, in the right anterior cerebral artery, located close to the internal carotid, and accompanied by an extensive subarachnoid hemorrhage. At the age of 3 years, the child had been affected with diphtheria, and for the last six months she had complained of severe headaches. Microscopic examination showed defects of the media and inflammatory and degenerative changes. The defect in the median layer, not uncommonly observed at the point of division of arterial branches, consisted of separation of the muscular ring into single muscle bundles and fibrils, followed by complete absence of the muscular cell elements.

E. L. MILOSLAVICH.

PRESENCE OF TRACES OF METAL IN GUNSHOT WOUNDS. GERHARD BUHTZ, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:609, 1932.

Spectrographic examinations of gunshot wounds, particularly of the ring of contusion and of the smudge, in instances of wounds produced by lead bullets, invariably disclosed presence of lead. The amount of lead was proportionate to the size of the caliber and to the range of distance; the smaller the bullet and the greater the distance, the less was the quantity of the lead demonstrable. Presence of copper is characteristic of a shot discharged at close range. If the caliber of the pistol is known, one is able to determine from the amount of copper present in the inlet wound the distance from which a projectile was fired.

E. L. MILOSLAVICH.

FATAL POISONINGS WITH APIOL IN CRIMINAL ABORTIONS. HANS KRANKAUER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:626, 1932.

Reports of severe poisonings with apiol (parsley camphor) are appearing in European literature. Two fatal cases are described, involving young women who took apiol as an abortifacient. The autopsies revealed severe hemorrhagic nephritis, methemoglobinemia and fatty degeneration of renal and hepatic parenchymas. Apiol is an extract of Fructus petroselini and was known to the ancients as an abortifacient. It is a dangerous drug, which causes marked damages to the red blood cells and degenerative changes, particularly of fatty character, in the parenchymatous organs, especially in the liver.

E. L. MILOSLAVICH.

Technical

THE TRYPTOPHAN TEST IN TUBERCULOUS MENINGITIS. HENRY H. LICHTENBERG, Am. J. Dis. Child. **43**:32, 1932.

Of seventy-eight spinal fluids subjected to the tryptophan test, all (twenty-five) from cases of tuberculous meningitis, proved either by autopsy or guinea-pig inoculation, were positive. Of the fluids showing a negative reaction, none was

demonstrated to be from patients having tuberculous meningitis. Purulent, xanthochromic and hemorrhagic fluids gave a false, but distinguishable, positive reaction. The test was of value as a diagnostic aid in the differential diagnosis of tuberculous meningitis and conditions that simulated it clinically or in spinal fluid findings.

AUTHOR'S SUMMARY.

A POTATO-EGG MEDIUM FOR THE ISOLATION OF TUBERCLE BACILLI. J. S. WOOLLEY and F. G. PETRIK, Am. Rev. Tuberc. **24**:596, 1931.

The authors describe a solid medium, consisting essentially of glycerinated potato extract in an egg base, for isolating tubercle bacilli from contaminated material. Similar results were obtained with either alkaline-treated or acid-treated sputum, but the alkaline method of digestion is preferred. It is necessary to seed at least twenty tubes of this medium to equal guinea-pig inoculation when the animal receives considerable amounts of material. However, positive results can be determined more readily and earlier by the culture method than by inoculation.

H. J. CORPER.

VITAL STAINING METHODS WITH NEUTRAL RED APPLIED TO NERVE DEGENERATION IN POLIOMYELITIS. W. P. COVELL and J. L. O'LEARY, Arch. Neurol. & Psychiat. **27**:518, 1932.

The authors point out the advantages of vital staining of sectioned nerves with neutral red. This was used either by the method of perfusion (the dye was allowed to pass into the aorta for about twenty minutes), by intravenous injection or by immersion. Often combined methods were used. The appended colored pictures show beautifully the condition of the myelin and of the axon, the vacuoles and granules of the histiocytes and the Schwann cells. The disadvantage of the method is the inability to retain permanent preparations of the experimental material, but it is a "valuable adjunct to the Marchi and Weigert procedures for the study of wallerian degeneration."

GEORGE B. HASSIN.

EGG YOLK AGAR IN CULTURE OF TUBERCLE BACILLI. R. D. HERROLD, J. Infect. Dis. **49**:420, 1931.

Further observations on the isolation of tubercle bacilli from sputum and other tuberculous specimens are recorded. The yolk of one egg is added to about 150 cc. of 1 per cent agar. Citric acid is added to the samples of urine and sputum to control contaminations. The egg yolk medium is particularly efficient in yielding a positive growth of tubercle bacilli from specimens found to be negative by repeated smears. The medium appears to be favorable for the rapid isolation and growth of tubercle bacilli.

EDNA DELVES.

CULTURAL AND IMMUNOLOGICAL METHODS OF DIAGNOSING INFECTIONS WITH ENDAMOEBA HISTOLYTICA. B. K. SPECTOR, J. Prev. Med. **6**:117, 1932.

The following medium is highly satisfactory for growing E. histolytica: slants prepared from 3 parts of inactivated human serum that has given a negative Wassermann reaction and 1 part of 0.85 per cent sodium chloride, overlaid with a mixture of 1 part of sterile inactivated human serum that has given a negative Wassermann reaction and 6 parts of either sodium chloride or Ringer's solution. In the detection of infections with E. histolytica, cultural methods are probably superior to direct fecal examinations. A negative result in the complement-fixation test for E. histolytica does not always signify the absence of infection with E. histolytica, because persons vary in the formation of complement-fixing antibodies, and because treatment with emetine sometimes alters the reaction. Likewise, a positive result may not signify infection with E. histolytica. Skin and precipitin tests are, as yet, inadequate for the diagnosis of infections with E. histolytica.

AUTHOR'S SUMMARY.

Society Transactions

PHILADELPHIA PATHOLOGICAL SOCIETY

Regular Meeting, March 10, 1932

V. H. Moon, *President, in the Chair*

Ectopia Cordis—Demonstration of a Case. Charles L. Lintgen.

A moving picture demonstration was given of a new-born infant exhibiting the following congenital anomalies—ectopia cordis, talipes varus (left), bilateral cleft palate, craniorachischisis, facial hemiatrophy and an unusually short umbilical cord (4 in. [10.16 cm.]). The mother was 25 years old and had had one normal child in 1929. The child with the anomalies lived for several hours. The heart projected prominently through the anterior wall of the chest, covered only by a thin, translucent membrane. The moving pictures demonstrated its contractions and enabled one to follow the sequence of auricular and ventricular systoles.

Lymphosarcoma with Unusual Metastases in a Thirteen Months Old Infant. P. L. Davis.

The lymphosarcoma took origin in the retroperitoneal chain of nodes, with metastases to the liver, to the epidural region of the cranium and, to a lesser extent, to a lung, a rib and a kidney. The cranial metastasis was the source of extremely puzzling clinical manifestations. Only at necropsy was the nature of the disease made clear. The infant was normal, born at full term and delivered normally, and was breast fed. During the first six or eight months the child did not seem as alert and active as the mother's previous children. She prided herself, however, on its apparent good nourishment, especially the round, protuberant abdomen, the contour of which was occasionally the topic for jest. When the child was 9 months old, enlargement of the cervical glands was manifest. At about the same time the mother was disturbed by frequent shrill cries of the baby during its sleep and by its fretfulness. Soon she noticed that it would fall to the right side. The right ear became more prominent than the left. In September, 1931, the child was brought to the Laryngeal Clinic of the Philadelphia General Hospital. Examination showed bulging of the posterosuperior wall of the right external auditory meatus. The tympanic membrane was not visible. Right facial paralysis of the peripheral type was noted. The laboratory findings were negative. The roentgen diagnosis was right subacute mastoiditis. The following day simple mastoidectomy was performed. No pus was obtained on opening the mastoid cells. A subsequent neurologic consultation suggested subdural abscess. Two weeks later ophthalmologic examination showed marked left exophthalmos and beginning right optic atrophy. Attention was given at this time to the cervical adenopathy. Several small doses of filtered x-rays were applied to the nodes, and under this treatment they promptly melted away.

The general condition gradually grew worse. On Jan. 18, 1932, a radical mastoidectomy was performed and necrotic bone removed from the right mastoid process. Culture showed a hemolytic streptococcus, but no pus was obtained. Neurologic signs of an involvement of the peripheral cranial nerves became obvious. Dysphagia necessitated nasal feedings. Right exophthalmos developed on Feb. 11, 1932, and dilated retinal veins and optic atrophy were prominent on examination of the eye-grounds. The child became extremely emaciated and died, Feb. 14, 1932.

After death there were found markedly enlarged retroperitoneal lymph nodes, particularly in the region of the head of the pancreas, although not invading the parenchyma of that organ. This seemed to be the primary seat of the tumor. The nodes were moderately firm and yellowish white. Their parenchyma was homogeneous and succulent, and the cut surface bulged. The chain extended cephalad as far as the hilus of the liver. The liver extended 10 cm. below the costal margin. Many irregularly rounded, firm nodules projected from its surface. On the posterolateral surface of the right lobe was a saucer-shaped concavity of large size. A cut section of the right lobe showed this concavity to be underlaid by a huge tumor mass occupying nearly the entire right lobe. Considerable central degeneration with mottled areas of hemorrhage and necrosis and a certain amount

of radial fibrous trabeculation were present. The periphery of the large mass resembled the tissue in the lymph nodes as did the cut surface of the smaller metastatic nodules. Further metastases were present as small nodules in the right kidney, the right seventh rib and the right lung. A retropleural lymph node was also involved. The epidural space of the right middle fossa was the seat of infiltration by tumor tissue to a thickness of 2 cm. The inner plate of the skull over the middle ear and mastoid regions was eroded, and the operative wound was in direct communication with the tumor mass. The right orbital fossa was also invaded. Through this epidural tumor mass the majority of the right cranial nerves must necessarily have passed to their exit from the skull.

Microscopically, the tumor cell throughout was the lymphocyte of adult form. In other words, the growth was a lymphosarcoma; subgroup, malignant lymphocytoma. Sections through the retroperitoneal nodes showed the architecture to be completely obliterated, the nodes being transformed into homogeneous cell masses. The stroma consisted of a delicate reticulum that divided the tumor cells into faintly discernible alveoli. The capsule of the node was infiltrated by tumor cells. The liver showed massive replacement of parenchyma by lymphocytic invasion. The smaller nodules were densely cellular; their immediate periphery showed tumor clumps within lymphatic channels and portal vein radicals, thus establishing a dual metastatic spread. The massive lesion in the right lobe of the liver was the seat of considerable central degeneration and fibrosis. The extent of the fibrosis suggested that the metastatic lesion here was of comparatively long duration, undoubtedly months. The spleen was uninvolved in the process. Sections through the skull overlying the right middle ear and mastoid process showed extreme infiltration by tumor cells, which were undoubtedly blood-borne to this situation, as evidenced by cell masses in veins and blood sinusoids of the marrow cavity. A rather marked fibrous osteitis was present, a reaction to the presence of tumor.

ALYMPHOID LEUKOPENIA AND PURPURA HEMORRHAGICA WITH AN ACUTE MILIARY EXACERBATION OF CHRONIC PULMONARY TUBERCULOSIS. HAROLD W. JONES, LEANDRO M. TOCANTINS and BAXTER L. CRAWFORD.

A girl, aged 15, was admitted to Jefferson Hospital in critical condition from epistaxis, long, profuse menstrual periods and a transfusion reaction. There was no history of tuberculosis in the family or in the girl. There was, however, a history of bruising and nosebleed in both parents and of nosebleed in the girl before her menstrual periods started. Three months before admission bruising was extensive. In spite of repeated blood transfusions, liver, liver extract, iron, a diet high in vitamin and high in protein, and roentgen treatment of the long bones and spleen, the condition became progressively worse; evidences of left-sided pneumonia developed, and the patient died two and a half months after admission.

From the day of admission there was marked leukopenia. The white blood cell count varied from 1,150 to 400, the smaller count being present at the termination of the illness. Contrary to the usual finding, the lymphocytes were greatly diminished, being always below 10 per cent and sometimes absent, and the granulocytes were more than 90 per cent and at times 100 per cent of the white blood cells.

Autopsy.—Slight generalized jaundice and marked anemia were found, with subcutaneous and subserous petechial hemorrhages and hemorrhages in the ovaries. There was a rather extensive tuberculous lesion in the left lung. In the apex were a small, contracted scar and a small encapsulated, caseous nodule, with numerous miliary and conglomerate foci throughout the lung; no cavitation was seen. The right lung also contained many miliary tubercles. The spleen weighed 80 Gm.; on microscopic examination the fibrous tissue was slightly increased, and the follicles were atrophic. No normal follicles with definite germinal centers were observed. Several tuberculous ulcers were found in the ileum. The liver weighed 1,230 Gm., and microscopic examination revealed considerable degeneration of the epithelial cells and beginning fibrosis with proliferation of the bile ducts, but very little evidence of leukocytic infiltration. The bone marrow of both the tibia and the femur was found to be entirely fatty, and microscopic examination

revealed that it was hypoplastic, with no evidence of hyperplasia of the hematopoietic cells. No megakaryocytes were found.

(The history of the association of tuberculosis and purpura from an experimental and clinical standpoint is discussed. It is set forth that tuberculosis is commonly found in cases of purpura hemorrhagica, and that many of the fulminating cases, so-called essential types, would be found to be associated with tuberculosis if a postmortem examination were made.)

The interesting points are a family history of bruising, nosebleed and long menstrual periods, the history of nosebleed in the patient before menstruation began, of long profuse bleeding when it became established, and of bruising and nosebleed before there was clinical evidence of tuberculosis. There was a comparatively high platelet count in the absence of megakaryocytes in the bone marrow. The bleeding time was greatly prolonged (thirty-one minutes), with a platelet count of about 100,000. A marked leukopenia was present with a high granulocyte count and an absence or a great reduction of lymphocytes.

We are unable to explain the phenomena presented on the basis of our clinical and pathologic findings. We suggest the name "alymphoid leukopenia" for this condition. Such a title is as applicable in this case as is "agranulocytic angina" or "anemia" for the condition described by Schultz and others.

Regular Meeting, April 14, 1932

The Annual Conversational Lecture was given by Dr. Arthur I. Kendall, of Northwestern Medical School: "Observations on the Significance of Filtrable Bacteria."

Regular Meeting, May 19, 1932

COMPARATIVE PATHOLOGY OF ARTERIOSCLEROSIS. HERBERT FOX.

(A lantern slide demonstration of arterial lesions occurring in many species of mammals, birds and reptiles was given. The material was largely drawn from necropsies at the Philadelphia Zoological Garden.)

GASTRIC ULCER IN CAPTIVE WILD ANIMALS. HERBERT L. RATCLIFFE.

Ulcerative lesions of the mucosa and wall of the stomach and duodenum, closely similar in gross and microscopic appearance to those in man, are found in many types of mammals. The records of the Laboratory of Comparative Pathology of the Philadelphia Zoological Society show that this disease has occurred in approximately 1 per cent of 5,000 mammals. Carnivora and Primates are most frequently affected, but gastric ulcer has been seen also in Marsupialia and Artiodactyla. Birds have not been affected. The ulcers have much the same anatomic distribution, and the behavior is also much the same as in man. Fatal hemorrhage, perforation with peritonitis or healing with radiating scar formation has been observed. The specimens exhibited illustrated these features.

RUPTURE OF THE ESOPHAGUS. A REPORT OF TWO CASES. A. D. WALTZ, CLARA I. DAVIS and R. P. REGESTER.

A thorough search of the literature on rupture of the apparently healthy esophagus reveals reports of only thirty-four cases. The earliest is that of Admiral Baron von Wassenair reported by Boerhaave in 1724. Full reviews of the subject may be obtained from articles by E. J. McWeeney (*Lancet* **2**:161, 1900) and H. T. Williams and William Boyd (*Surg., Gynec. & Obst.* **42**:56, 1926).

CASE 1.—A colored woman, aged 55, was admitted to Delaware County Hospital on Jan. 16, 1931, in the service of Dr. R. P. Regester. The patient had seldom been sick, having had only one (slight) attack of indigestion one year before. She said she did not use alcohol and tobacco. Her illness, lasting thirteen days, began one evening with acute pain in the upper part of the abdomen, following a meal of stewed beef. The patient took magnesium sulphate and two acetylsalicylic

acid tablets, which were immediately vomited. Vomiting continued intermittently all night and the following morning, but the pain disappeared. The vomitus was greenish. There was no hematemesis. Examination revealed an obese colored woman in semistupor. The pupils reacted normally to light. The breath had a foul odor, and the pharynx was slightly congested. The neck was normal. There were no adventitious signs in the lungs. The heart was regular, rapid and difficult to outline. The abdomen was tender and slightly rigid in the hypochondrium. The blood pressure was 200 systolic and 110 diastolic. A tentative diagnosis of acute disease of the gallbladder was soon changed to meningococcic meningitis. The patient grew worse and died suddenly on Jan. 29, 1931. At autopsy, in addition to the usual lesions of meningococcic meningitis, the esophagus was found ruptured (4 by 1.5 cm.) on its left side above the diaphragm. The surrounding tissue showed no inflammatory change, but the edges of the ruptured portion were necrotic. The left pleural cavity contained 500 cc. of thin, dark red fluid similar to that found in the stomach.

Case 2.—A white woman, aged 27, was admitted to Delaware County Hospital, Feb. 7, 1932. The patient had been delivered one month previously of a child who died of syphilis and a hemorrhagic disorder. The onset of the present illness occurred three days after a second injection of 0.3 Gm. of neoarsphenamine. The patient felt as though she were becoming "wild" and returned home screaming. At this time the family physician carried on artificial respiration. The left pupil was dilated. She felt well the following morning, but fell asleep that afternoon on taking ¼ grain (0.016 Gm.) of phenobarbital and 1 grain (0.06 Gm.) of phenobarbital sodium. She presented the picture of deep drug narcosis. The entire body was covered by a macular rash. The heart was fibrillating. The heart sounds were harsh, and a few râles could be heard in both bases. The abdominal findings were negative except for slight distention of the abdomen. All reflexes were absent. The patient never regained consciousness, and died nine and one-half hours after admission to the hospital. Autopsy soon after death showed a linear rupture of the esophagus 7 cm. in length just above the diaphragm. There was 350 cc. of dark brown fluid in the left pleural cavity, also similar fluid in the stomach. The right pleural cavity was normal. The remaining organs show marked toxic degeneration.

A Severe Case of Alkalosis. A. I. Rubenstone and Jacob Levy.

A Russian Jewess, 29 years old, was delivered of a 1½ pound (453.6 Gm.) fetus at the end of six and one-half months of gestation. She had shown symptoms of toxemia throughout this and a previous pregnancy. Five days after delivery she had lapsed into stupor from which she aroused at intervals. Examination of the blood revealed a carbon dioxide content of from 108 to 114 per cent by volume. The blood chlorides amounted to 384 mg. and the nonprotein nitrogen to 63 mg. per hundred cubic centimeters. The stupor deepened in spite of energetic treatment. Marked cyanosis and muscular twitching developed shortly before death. Attention is called to the fact that persons exhibiting symptoms often referred to acidosis may have alkalosis.

A Case of Primary Squamous Cell Carcinoma of the Thyroid Gland. A. I. Rubenstone and D. R. Meronze.

A white woman of 55 years complained, on Nov. 8, 1930, that for several months she had been conscious of a "tightening" sensation on swallowing. This had increased until she found it difficult to swallow liquids. Physical examination revealed an enlarged, irregular left lobe of the thyroid gland, which was hard and nodular, with deviation of the trachea to the right and compression, and paralysis of the left vocal cord. On December 10, approximately three months after the onset of the symptoms, she was admitted to Mount Sinai Hospital. At this time loss of weight was noted. The trachea was fixed, and esophagoscopy revealed an infiltrative lesion of the upper part of the esophagus, but without ulceration. Biopsy proved the lesion to be a squamous cell carcinoma. The patient's condition became rapidly worse. She died on Jan. 24, 1932, one week after an emergency tracheotomy.

Primary carcinoma of the thyroid gland is a relatively uncommon condition. In a series of 6,535 thyroid glands operated on and examined at Lahey Clinic in Boston between 1916 and 1930, 187, or 2.86 per cent, showed primary malignant growth. In this group only one showed a squamous cell carcinoma. The tumor presented here, we believe, is a primary squamous cell carcinoma.

At autopsy, the area normally occupied by the left lobe of the thyroid gland was filled with a large quantity of necrotic, grayish material, alternately composed of soft and hard masses of tissue, in the midst of which were several hard, white, homogeneous areas. The left sternocleidomastoid muscle was adherent to this area. The muscle was hard and apparently infiltrated, forming a firm mass with the regional blood vessels and lymph nodes. The right side grossly appeared relatively normal, but on section it was also seen to be partly replaced by a hard, white, homogeneous tissue of the same kind as that seen on the left side. A large mass of glands on the right side of the trachea were hard in consistency and on section showed a white, homogeneous appearance. The tumor mass infiltrated and projected into the upper part of the esophagus from without. The lower portion of the esophagus was normal. An obstruction was met, on entering the esophagus from above, at the level of the cricoid cartilage. This obstruction was due to a deviation of the pharynx to the left, causing narrowing and kinking of the esophagus. The first two tracheal rings felt softer than normal, and there was marked narrowing of the lumen in this region, caused by deviation of the trachea to the right. The rima glottidis was closed by a swelling in the region of the left arytenoid cartilage. On incision, the entire mechanism of the larynx was distorted by a mass involving the left side. The mass bulged the wall forward, filling the lumen and displacing the left vocal cord upward and posteriorly. This mass was in the thyroid cartilage and was part of the mass described as replacing the left lobe of the thyroid gland. It had a hard, white, homogeneous appearance on section. It had destroyed a large part of the cartilaginous tissue. There was no break in continuity in the mucosa lining the larynx. Metastatic lesions were also found infiltrating the spleen.

Histologically, the tumor involved the thyroid gland, larynx, mediastinal contents and esophagus. The cells were polyhedral and flattened in shape, such as are seen in squamous epithelial tumors. Their nuclei were large, contained nucleoli and often showed mitoses. Occasionally they formed small, glandlike structures, but in the great majority of instances they formed solid cores or lobules. Prickles could not be identified, but there were large numbers of epithelial pearls. In some regions these cells penetrated connective tissue, itself infiltrated with round cells and polymorphonuclear leukocytes. One section from the thyroid gland showed the malignant growth infiltrating normal thyroid tissue.

From the clinical report it will be seen that the tumor did not spring from the esophagus or from the trachea. This opinion is further substantiated by the gross findings at autopsy in which no lesion was seen arising in the esophagus or in the remainder of the gastro-intestinal tract or in the pulmonary system. The tumor masses compressed the esophagus and trachea from without. No other tissue where a malignant condition was found in this particular case could be considered a primary site. The integrity of the skin, which was carefully examined, precludes an assumption that it originated from the integument of the neck. There still remains the possibility of an origin from a branchial remnant.

The diagnosis of branchiogenic carcinoma after it has advanced to the cervical lymph nodes may be difficult. It should be emphasized that the usual form of the tumor is a cystic growth in and about which are carcinomatous areas, and that most cases are encountered when the cysts are recognizable, and when a squamous cell cover is present or predominant. We believe that this is not a tumor of this sort because it lacks the cystic quality of the usual branchiogenic tumor, because none but epithelial tissues were found therein, and because from the earliest symptoms the major tumor mass was in the thyroid gland. Having eliminated other local sites as possible sites of primary squamous cell carcinoma, we conclude that the case is an instance of primary squamous cell carcinoma of the thyroid gland, probably arising from the thyroglossal duct.

Book Reviews

Recent Advances in Pathology. By Geoffrey Hadfield, M.D., F.R.C.P. (Lond.), Professor of Pathology in the University of London, Pathologist to the Royal Free Hospital, and Lawrence P. Garrod, M.A., M.B., B.Ch. (Camb.), M.R.C.P. (Lond.), Bacteriologist and Lecturer in Bacteriology, late Demonstrator of Pathology, St. Bartholomew's Hospital. Price, $3.50. Pp. 392, with 67 illustrations. Philadelphia: P. Blakiston's Son & Co., 1932.

The series on "Recent Advances in Pathology" has grown rapidly. It now includes twenty-five volumes, representing different phases of medicine. All the volumes are products of British authors. The volume by Hadfield and Garrod presents a survey of recently acquired knowledge bearing on fundamental problems connected with a number of specific diseases. The first chapter deals with the reticulo-endothelial system, its composition, functions and relation to immunity, metabolism of bile pigment and certain splenomegalies. Then comes a review of tissue culture and its uses. The next four chapters are concerned with research on cancer: carcinogenesis by irritants, transplantation, filtrable tumors, tumor metabolism, heredity and the actions of roentgen rays and radium. A clear account is given of the discovery and properties of the vitamins, with a discussion of the deficiency diseases, hypervitaminosis and calcium metabolism. In the realm of the cardiovascular system, endocarditis, especially the rheumatic and infective types, and diseases of the arteries receive special attention. The account of experimental endocarditis does not stress sufficiently the establishment by Rosenow and other experimenters of endocarditis by intravenous injections of bacterial suspensions only. The respiratory system is represented by surveys of pneumonia, principally its experimental production, of primary carcinoma of the lung, of the pneumonoconioses and of anoxemia. The chapter on the digestive system deals with peptic ulcer, necrosis of the liver, the changes in the pancreas in diabetes and the islet tumors. The recent work on Bright's disease receives consideration. In the case of the central nervous system, the newer work on the neuroglia and the glioma group of tumors as well as on the problem of encephalitis is reviewed. The last chapter is devoted to the thyroid, the parathyroids and the suprarenals. There are an index of subjects and one of authors. At the end of each section is a list of references for guidance to important recent publications. In the text are helpful summaries and tabulations. The authors have succeeded in writing good reviews of recent significant work in the fields mentioned.

Entstehung, Erkennung und Behandlung innerer Krankheiten. By Dr. Ludolf Krehl, Professor in Heidelberg. Erster Band. Die Entstehung innerer Krankheiten: Pathologische Physiologie. Fourteenth edition. Price, 39.60 marks. Pp. 716. Berlin: F. C. W. Vogel, 1932.

This is Krehl's "Pathologische Physiologie" dressed up in a new garb as "Die Entstehung der innerer Krankheiten." The preceding edition first bore this new title and was published as one of three volumes designed to embody the principles of the practice of internal medicine. Two are available; the third, devoted to therapy, will soon be at hand. This volume has had a long and successful career. It was first published in 1893, as "Grundriss der allgemeinen klinischen Pathologie." Translations soon appeared in French, Russian, Polish and other languages; the third German edition was translated into English by Hewlett; a subsequent translation into English was made by Beifeld from the seventh German edition. It is singular that the author's prefaces contain no statements reflecting satisfaction with his accomplishment. The preface for this last edition is a reprinting of that in the thirteenth, to which a short note has been added. In the latter, he says,

no one knows as he does how far the book falls short of his ideals. This is certainly an unusual humility, judged by his results during almost forty years of steadily improving an achievement successful in the first place. In an introductory note to Hewlett's translation (1906), Osler commented on the position the "Clinical Pathology" then occupied: "Not that it needs any words of commendation," an encomium even more justifiable now.

In the first edition the chapters were on the circulation, blood, respiration, digestion, metabolism, fever, urinary excretion and the nervous system. These have been retained throughout the numerous editions and have gradually been added to, so that now there are also chapters on endogenous disease and constitution, infection and immunity, origin of infectious diseases, energy exchange, water and salts in the body (mainly a discussion of edema) and coordinate functioning of the organs. Changes from the edition of two years ago are not significant, simply those one expects in a well established book maintaining its position as a staple commodity in medical literature: A paragraph has been added here and there which discusses the results of recent investigation; there are occasional new sentences to express the author's previous opinion in more vigorous terms; about thirty pages have been added, there is a more comprehensive list in the table of contents of matters considered in each chapter, and all of the familiar aspects of arrangement and printing have been retained.

Overcrowding of undergraduate instruction with objective description, summaries of facts and laboratory methods has left little room in the student's regimen for textbooks largely devoted to principles. This probably accounts for some restriction, indeed deplorable, of the rôle Krehl's book has upheld, so preeminently a reference work for clinicians and an exegesis for the physician's hour of leisure. In the domain of the purely morphologic, great difficulty has always been experienced in so presenting disease that its somatic structural modifications may be visualized. To comprehend the manner in which disease in its functional disturbances also involves the entire body is an even larger undertaking. The chief value of this, Krehl's masterpiece, is its dedication to that object in so large a measure. For this reason alone its use by medical students should be extended. In other fields its value has been fully realized.

The Sign of Babinski: A Study of the Evolution of Cortical Dominance in Primates. By John F. Fulton, Sterling Professor of Physiology in the Yale University School of Medicine, and Allen D. Keller, Professor of Physiology and Pharmacology in the School of Medicine, University of Alabama. Price, $5. Pp. 165, with 66 illustrations. Springfield, Ill.: Charles C. Thomas, 1932.

This research presents an experimental approach to a major pathologic problem which is unusual in method and results. The method employed is unusual because of its cost in time and in money; the results achieved are unusual because of the rare competence of the authors in neurophysiology, in surgical technic and in critical acumen. The Babinski reaction is one of the most important signs employed in clinical neurology; just what it means is still controversial, and this study takes one far toward a solution of the problem.

The account begins with a reproduction and translation of Babinski's original description of 1898. The scanty comparative data in the subsequent literature indicate that the true Babinski reflex is seen only in the primate foot. The authors have studied it experimentally in several species of long-tailed monkeys, twenty-two baboons, two gibbons and nine chimpanzees, with a critical survey of previous experimental work on primates. These experiments included semisection and transection of the spinal cord at various levels, electrical stimulation of the cortex, ablation of one or both leg areas of the cortex, complete removal of one cerebral hemisphere and various combinations of these operations. In the spinal monkey the Babinski phenomenon, when present, is part of a generalized flexion reflex. In these monkeys no Babinski reflex is obtained from cortical destruction of the pyramidal tract; the reaction is thus not solely an affair of the

pyramidal pathways. In the baboon and gibbon, there is a progressive change in the conditions which evokes this sign until in the chimpanzee a true Babinski response can be obtained after ablation of the leg area of the cortex. Other signs of degeneration of the pyramidal tract are described and discussed. "In the higher primates the sign of Babinski is associated with isolated destruction of the pyramidal pathways." In the large apes the cortical leg area exerts some measure of control over the musculature of the same side of the body.

The clinical implications are discussed, especially in traumatic cerebral diplegia, Little's disease and spinal shock. "It is obviously significant that a cortical lesion in the higher primates resembles spinal 'shock' more closely than in the lower primates, and it serves to illustrate in dramatic fashion the process of encephalization in primate evolution. In man the dominance of the hemisphere is so complete that simultaneous destruction of both foot areas is virtually equivalent, as far as motor power of the lower extremities is concerned, to spinal transection." The book closes with an appendix on surgical technic, a bibliography (114 titles) and an index.

Techniques de laboratoire appliquées aux maladies de l'appareil digestif et de la nutrition. By Marcel Labbé, Membre de l'Académie de Médecine, Professeur de Clinique médicale à la Faculté de Médecine de Paris, Henri Labbé, Professeur agrégé, Chef de travaux pratiques de Chimie à la Faculté de Médecine de Paris, and Floride Nepveux, Chef de Laboratoire à la Faculté de Médecine de Paris. Paper. Price, 140 francs. Pp. 886, with 141 illustrations and charts and 6 colored tables. Paris: Masson & Cie, 1932.

This book is the outcome of a course given by the authors since 1900 at the medical faculty of the University of Paris. One of the authors is a clinician; the others are laboratorians. The responsibility for the various chapters is divided. The book gives a great deal more than is indicated by the title. It represents, in reality, a complete treatise on physiologic chemistry in 360 pages, as well as a detailed outline of laboratory technic in the remaining 507 pages.

The theoretical chapters, which present the important modern conceptions on the various phases of the subject, are made particularly interesting by the critical attitude of the authors. The pros and cons of each controversial question are followed by the personal views of the writers. In the chapters devoted to technical procedures, the critical attitude is still more pronounced. It is quite apparent that their preference for certain procedures and the rejection of others are based on personal experience of many years. In other words, the book is not merely a compilation of various laboratory tests, but a critical evaluation of procedures which stood the acid test of clinical application.

The examination of the gastric and duodenal contents is discussed in 17 and 18 pages, respectively, followed by 264 pages devoted to an extremely thorough presentation of tests employed in the examination of urine. The authors lay great emphasis on the value of quantitative chemical analysis of urine for the study of metabolic changes. When the reviewer compares the space given in this book to urinalysis with the tendencies in the majority of modern textbooks on laboratory procedures to emphasize the value of the chemical examination of the blood at the expense of the urinalysis, he welcomes the attitude of the French authors and believes with them that much direct information can be gained by the study of urine which is nowadays frequently arrived at by using roundabout, expensive ways.

In the chapter of 60 pages devoted to feces, as well as in the remainder of the book, the bacteriologic phases are considered merely in passing. In the last chapter the chemical analysis of blood is discussed in 134 pages. For some reason, which is not apparent to the reviewer, creatine and creatinine have been omitted from this technical chapter, though they were discussed in 3 pages in the theoretical part.

The size of the book is unnecessarily increased by numerous repetitions in the technical chapters of theoretical discussions of questions already exhaustively presented in the theoretical part of the book. An almost literal repetition of a paragraph on page 572 and a few errors in the numbering of figures were noticed. The absence of a subject index detracts considerably from the value of the book.

La maladie de Boeck: Sarcoides cutanées bénignes multiples. By Dr. A. Kissmeyer, Médecin de l'Institut Finsen. Preface by Dr. J. Darier. Pp. 147, with 67 illustrations. Copenhagen: Levin & Munksgaard, 1932.

Since Boeck, in 1897 at Christiania, first described the skin disease which bears his name, it has been a matter of great speculative etiologic interest to dermatologists.

Kissmeyer, who has devoted several years to the study of cutaneous and other sarcoids, bases his monograph on 28 personal cases of Boeck's disease and 250 other cases reported in the literature. Under the caption of benign cutaneous sarcoid, he includes Besnier's lupus pernio, Pautrier's angiolupoid and a sarcoidic erythrodermia which seems to correspond to Darier's "erythematous tuberculids." Other forms, such as granuloma annulare, are questionably omitted. Generally, he classifies Boeck's disease as a type of chronic infectious granuloma which involves not only the skin but also the mucosae, lymphatic system, parenchymatous organs, skeleton and the like. The usual clinical types — large and small nodular, disseminated and diffuse — are described.

The 23 short chapters which make up the monograph include the clinical descriptions of the various types and discussions of the various opinions held by different investigators.

In the chapter on histology, the principal point made is that the absence or only slight degree of lymphocytic reaction around the disease foci is almost pathognomonic of sarcoid, as well as the distinct limitation toward the surrounding tissues.

The chapters of greatest interest are those dealing with the etiology. Kissmeyer reviews Boeck's changing attitude toward what he considered the nature of the disease, and also the views of Darier, Kyrle and others who supported or denied its tuberculous origin. Some of the patients studied by these authors were unquestionably tuberculous apart from the sarcoid. In only 6 of 150 cases critically studied by Kissmeyer was there an unquestionable tuberculosis. Therefore, on this account, as well as because of his failure in any of his own cases to demonstrate the tubercle bacillus by any of the known clinical or biologic tests, he expresses the opinion that when a cutaneous disease the virus of which is not yet known gives a negative or weak reaction with great regularity, a tuberculous origin is improbable. In his introduction, however, Darier points out that this does not exclude a filtrable form of the bacillus.

The fact that the author's tests of the blood and diseased tissues for the tubercle bacillus were 100 per cent negative is strong evidence against the view, now commonly held in textbooks and elsewhere, that Boeck's sarcoid of the skin is of tuberculous origin. He considers his view strengthened by the fact that in his cases arsenic was the drug which gave the best results; it is of little value in cutaneous tuberculosis.

Kissmeyer further finds that the cutaneous and osseous manifestations approximate the sarcoids to lepromas; there are as many clinical facts common to sarcoid and leprosy as to sarcoid and tuberculosis.

As a conclusion, Kissmeyer thinks that in the absence of a specific virus Boeck's disease cannot yet be definitely classified among the chronic infectious granulomas. It should be placed between tuberculosis and leprosy.

Kissmeyer's monograph, while it leaves matters still unsettled, nevertheless is an important contribution which must be referred to by all future workers on this puzzling condition.

Special Cytology. The Form and Functions of the Cell in Health and Disease. A Textbook for Students of Biology and Medicine. By Various Contributors. Edited by Edmund V. Cowdry, Washington University, St. Louis. In 3 volumes. Second edition. Fabrikoid. Price, $30 per set. Pp. 1838, with 757 illustrations. New York: Paul B. Hoeber, Inc., 1932.

The first edition of this work appeared in the early part of 1928 and was reviewed favorably in the ARCHIVES (**5**:1152 [June] 1928). The second edition is an impressive improvement and expansion of the first. The number of volumes has been increased from two to three, and the price accordingly from $20 to $30 for the set. The original sections have been revised by their authors, and in some cases have been completely rewritten in order to reflect more adequately the recent advances of knowledge in the special fields. The section on the lymphocytes and plasma cells by the late Alexnder A. Maximow has been revised by W. Bloom. The major part of the increase in the size of the second edition is due to the inclusion of new sections to cover subjects not previously considered, namely: human uterine gland cells by C. W. Bartelmez and R. R. Bensley; the gastric glands by R. R. Bensley; cartilage and bone by A. W. Ham; the spleen by P. Kyes; ciliated epithelium by A. M. Lucas; the cornea and lens by Ida Mann; architecture of nerve cells as revealed by microdissection by G. S. de Renyi; the suprarenal bodies by J. M. Rogoff; bone marrow by Florence R. Sabin; the teeth by J. Schour; the hair by Mildred Trotter, and the capillaries by A. Krogh and B. Vimtrup. The work now contains forty-four sections by forty-six contributors, about twenty-six of whom are anatomists. Each section is provided with a list of contents at the beginning and a bibliography, sometimes quite extensive, at the end. Through the three volumes the pagination runs consecutively. The third volume contains the index. The main topics in each volume are given on its back, and it would have been helpful to the reader if the pages included in the volume had been given also. The illustrations, almost exclusively black and white, are adequate and commendable. Elaborate descriptions of specialized technical details are avoided, but the results of the intensive study of the cells and cellular activities by modern technics are presented in authoritative fashion by writers with intimate, first hand knowledge each of his own subject. Embryogenic cytology is not considered. Attention is directed mainly to the principal types of cells in the postembryonal human body. The work should be available to all students of normal and abnormal cytology.

Books Received

FUNGOUS DISEASES: A CLINICO-MYCOLOGICAL TEXT. By Harry P. Jacobson, M.D., Attending Dermatologist and Member of the Malignancy Board, Los Angeles County General Hospital. With Introduction by J. Frank Schamberg, M.D., Professor of Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania, and Howard Morrow, M.D., Clinical Professor of Dermatology, University of California Medical School. Price, $5.50. Pp. 290, with 153 illustrations. Springfield, Ill.: Charles C. Thomas, 1932.

VITAMINS: A SURVEY OF PRESENT KNOWLEDGE. Compiled by a Committee appointed jointly by the Lister Institute and Medical Research Council. Medical Research Council, Special Report Series, No. 167. Price, 6 shillings 6 pence, net. Pp. 319. London: His Majesty's Stationery Office, 1932. (It can be obtained from The British Library of Information, 5 East Forty-Fifth Street, New York.)

THE THIRD PANDEMIC OF PLAGUE IN EGYPT: HISTORICAL, STATISTICAL AND EPIDEMIOLOGICAL REMARKS ON THE FIRST THIRTY-TWO YEARS OF ITS PREVALENCE. By A. W. Wakil, M.B., Ch.B. (Cairo), Dip. Hyg. (Camb.), D.T.M. & H. (Camb.), Assistant Professor of Hygiene and Preventive Medicine Faculty of Medicine, Cairo. Pp. 169. Cairo: The Egyptian University, 1932.

CLASSIC DESCRIPTIONS OF DISEASE. By Ralph H. Major, M.D., Professor of Medicine, University of Kansas School of Medicine. Price, $4.50. Pp. 630. Springfield, Ill.: Charles C. Thomas, 1932.

THE SPUTUM: ITS EXAMINATION AND CLINICAL SIGNIFICANCE. By Randall Clifford, M.D., Associate in Medicine, Peter Bent Brigham Hospital; Assistant in Medicine, Harvard Medical School. Price, $4. Pp. 167, with 21 figures and 7 plates in color. New York: The Macmillan Company, 1932.

REPORT ON CHRONIC DISEASE IN NEW JERSEY. Made in Accordance with Joint Resolution No. 3, P.L. 1931. State of New Jersey, Department of Institutions and Agencies, Trenton, 1932.

UNITED FRUIT COMPANY MEDICAL DEPARTMENT: TWENTIETH ANNUAL REPORT. Boston, 1931.

CLINICAL ENDOCRINOLOGY OF THE FEMALE: By Charles Mazer, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania; Gynecologist to Mount Sinai and Northern Liberties Hospitals, Philadelphia; and Leopold Goldstein, M.D., Demonstrator of Obstetrics, Jefferson Medical College; Assistant Gynecologist to Mount Sinai Hospital. Price, $6, net. Pp. 518, with 117 illustrations. Philadelphia: W. B. Saunders Company, 1932.

AMERICAN ILLUSTRATED MEDICAL DICTIONARY: A COMPLETE DICTIONARY OF THE TERMS USED IN MEDICINE, SURGERY, DENTISTRY, PHARMACY, CHEMISTRY, NURSING, VETERINARY SCIENCE, BIOLOGY, MEDICAL BIOGRAPHY, ETC. By W. A. Newman Dorland, M.D., Member of the Committee on Nomenclature and Classification of Diseases of the American Medical Association. Edition 16. Flexible and stiff binding, plain, $7, net; thumb index, $7.50, net. Pp. 1,493 with 941 illustrations and 279 portraits. Philadelphia: W. B. Saunders Company, 1932.